Exhibit 160

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

MEMORANDUM OF TELEPHONE CONVERSATION

June 6, 1994

Between: Dr. Stephen Gettings
The Cosmetic, Toiletry, and Fragrance Association

and

Donald C. Havery
Chemist, Cosmetics Technology Branch, HFS-127
Office of Cosmetics and Colors

Subject: Talc

Dr. Gettings was called to obtain information on the identity and specifications for cosmetic grade talc. Dr. Gettings had presented a talk on this subject at the workshop entitled Talc: Consumer Uses and Health Perspectives, in January, 1994. Dr. Gettings told me that he would obtain the desired information from those knowledgeable in the talc industry and send me the information.

Donald C. Havery

cc:
HFS-100, Bailey
HFS-125, Dennis
HFS-127, Havery
HFS-128, Bronaugh

HFS-127: DCHavery:dch:6/21/94:205-4345

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

January 13, 1992

Dr. E. B. Ilgren
604 Fariston Drive
Wynnewood, PA 19096

Dear Dr. Ilgren:

This letter responds to your recent request for information concerning COSMETIC TALC, focusing upon its safety and toxicological properties as well as its "dusting" potential, dust concentration in the air, and aerodynamic characteristics of the particulates in the air. As I indicated to you during our recent telephone conversation, most of the available data about "dusting" of talc has been derived by means of animal studies in which human use conditions have only been modeled or approximated. Some human epidemiology studies involving the exposure of talc miners and ceramic pottery workers to talc dust and/or talc-containing "slip" have been reported. Some of this information is cited in the "Comments on Talc" section of the Tentative Final Monograph, "Skin Protectant Drug Products for Over-Counter Human Use; Diaper Rash Products; Proposed Rule" (c.f., FEDERAL REGISTER, 55 (No. 119), 25223-25225, June 20, 1990). Other relevant data and information on this subject can be obtained in the monograph "Criteria for a Recommended Standard... Occupational Exposure to Crystalline Silica" (HEW Publication No. NIOSH 75-120), which can be requested directly from the U.S. National Institute for Occupational Safety and Health, Technical Information Branch, 4676 Columbia Parkway, Cincinnati, OH 45226 (Telephone No. 513-533-8328).

I am pleased to be able to provide for your information a part of the abovenamed literature, in the form of the "Comments on Talc" excerpt, taken from the FEDERAL REGISTER citation given, which I am enclosing herein. Also, I am sending to you at this time an abridged bibliography addressing the literature of cosmetic talc. In doing so, this compilation is not exhaustive in its treatment of the subject, and we are continually updating and making additions to this literature database.

In closing, I trust that the literature provided will be of interest and value to you. Please feel free to contact this office again if I can be of further assistance to you.

Sincerely,

Stanley R. Milstein

Stanley R. Milstein, Ph.D.
Associate Director for Cosmetics
Division of Colors & Cosmetics (HFF-442)
U. S. FOOD & DRUG ADMINISTRATION

Enclosure

cc: HFF-400 (Mr. Burke)
HFF-440 (Dr. Bailey) ✓

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date February 10, 1994

From Robert L. Bronaugh, Ph.D. RLB
Jeffrey J. Yourick, Ph.D. JJY

Subject Report on Talc Workshop

To John E. Bailey, Ph.D.
Thru: D. Adele Dennis, Ph.D. DAD

A workshop was held January 31 - February 1, 1994 in Bethesda, MD entitled "Talc: Consumer Uses and Health Prospectives". The workshop was jointly sponsored by FDA and the International Society of Regulatory Toxicology and Pharmacology. It was attended by approximately 100 persons from government, industry and academia.

Introductory comments were made by Dr. John E. Bailey (CFSAN, Acting Director, Office of Cosmetics and Colors) and Dr. William E. Gilbertson (CDER, Director, Monograph Review Staff). Talc is contained in numerous products regulated by both FDA centers. The workshop focused on inhalation exposure to talc and the association of talc and ovarian cancer. Presentations were made by renowned experts in these fields.

The use of talc in cosmetic products was discussed by CTFA's Dr. Stephen Gettings. Cosmetic grade talc (mainly magnesium silicate) is considered to be 99% pure containing "200 mesh" or approximately 75 μm particles. Industry specifications of cosmetic talc state that the talc is free of asbestos and this is insured by industry quality control procedures (since the early 1970's). Dr. Gettings stated that the NTP inhalation study used talc particles of much smaller dimension (10 μm) and as such would be more available for inhalation to the deep lung than cosmetic grade talc.

It was estimated that application of body powder to an adult results in a respirable dust concentration of 1.0 mg/m^2. The ACGIH allowable value for industry talc dust concentration is 2.0 mg/m^2. A 2,000 to 20,000 fold higher exposure to talc was used in the NTP inhalation studies.

Inhalation Toxicity of Talc

Results from the NTP carcinogenesis bioassay of talc were presented by Dr. Gary Boorman (NIEHS). Male and female rats and mice of both sexes were exposed to two dose levels of talc over a period of approximately 2 years by the inhalation route (i.e., whole body). Pheochromocytomas were present, however, it was thought that these were not directly related to talc exposure. Tumors were discovered at the end of the study in lungs of female rats only. Dr. Boorman stated that mechanistic studies were needed to establish the relevance of the animal data when compared to potential human talc exposures at much lower levels. However, this caveat has not been included in the widely disseminated NTP bioassay report. For comparison to other compounds, it was noted that diesel exhaust, titanium dioxide and silica (all referred to as nuisance dusts with inert particle not chemical effects) have also resulted in tumor formation

predominately in female rats. It was suggested by several participants that talc may simply fall into the same category as an inert particle with nonspecific effects.

Presentations by Drs. Gunter Oberdörster (University of Rochester) and Jay Goodman (Michigan State University) contended that the dose of talc administered in the NTP bioassay was excessive. They felt that the high dose of talc that resulted in the rat lung tumors likely caused an overload on the body's defense mechanisms that would normally clear the lungs of inhaled talc. Dr. Oberdörster stated that the rat seems to be a sensitive species to the effects of particle overload and the formation of lung tumors. He stated that instead of the maximum tolerated dose (MTD), NTP should have selected the maximum sensible dose. Ideally this dose should have a minimal affect on the normal lung clearance of particles, i.e., talc. It was suggested that humans may not be susceptible to lung tumors resulting from particle overload based on data from the observation of coal miners. Dr. Goodman was the only dissenter on the NTP advisory panel that reviewed the bioassay results. He provided evidence from several cytotoxicity biomarkers that the high dose of talc exceeded that MTD since female mice developed chronic lung toxicity (hence questioning the relevance of the dose). In addition, he stated that the NTP talc control incidence for the pheochromocytomas was four-fold higher than the historical controls.

Dr. James Crappo (Duke University) stated that anatomical differences between rat and human lungs make it difficult to extrapolate linearly the effects of a toxicant. The structure of the upper respiratory track and lungs would facilitate greater uptake and deeper penetration of talc into the lungs of the rat.

Studies presented by Dr. Brooke Mossman (University of Vermont) showed that, in contrast to asbestos, talc had no hemolytic/membranolytic activity, little-to-no activity in genotoxicity tests and did not stimulate cellular proliferation.

Workshop Consensus

The general consensus of this workshop session was that the results from the NTP bioassay in rodents were not indicative of a human health hazard from the inhalation of talc in consumer products. It was suggested that the talc response observed was a nonspecific dust response due to a lung clearance overloading dose of smaller than cosmetic grade talc particles.

Ovarian Toxicity of Talc

Ovarian cancer is responsible for 6% of the yearly cancer fatalities in women according to Dr. Harland Austin (Emory University). Factors responsible for a decreased risk of ovarian cancer are: (1) use of birth control pills, (2) previous term pregnancies, (3) breast feeding, and (4) hysterectomy/tubal ligation. The risk of ovarian cancer increases as the length of a women's ovulatory life increases. Dr. Arnold Brown (University of Wisconsin) stated a belief in the association of ovarian cancer and talc exposure based on the 1971 report by Henderson which claimed to find talc deeply imbedded in ovaries following talc exposure. Other studies did not find a migration of talc particles outside of the lung or G.I. tract after inhalation or oral talc exposure, respectively. It is at present unclear as to a mechanism of talc migration to the ovaries.

Epidemiological studies of perineal talc exposure were discussed by Drs. Bernard Harlow

(Brigham & Woman's Hospital) and Patricia Hartge (National Cancer Institute). Dr. Harlow's study showed that daily application of talc perineally resulted in an odds ratio of 1.8 (95% confidence interval 1.1-3.0) for ovarian cancer. There was a modest increase in risk with years of exposure. The greatest cancer risk was seen in women with 10,000 or more lifetime talc applications during ovulatory periods (odds ratio 2.8, 95% confidence interval 1.4-5.4). Long-term exposure to talc before 1960, when asbestos fiber contamination of talc was more likely, posed an increased risk of ovarian cancer. However, these women were also at increased risk because of long-term usage of talc. Dr. Hartge reported that the appropriate odds ratio from the Harlow study should be 1.8 not the higher value of 2.8. She stated that the study demonstrated a weak association between the use of talc and ovarian cancer.

Dr. Ernst Wynder (American Health Foundation) commented on methods used in conducting epidemiological studies. He felt that more accurate information can be obtained from control subjects if they are also hospital patients with a similar disease (instead of volunteers selected from the community). He indicated that additional information on the current usage by women of products containing talc would be helpful in assessing the potential health hazard.

Workshop Consensus

The general consensus of this workshop session was that there is a weak association between the use of talc and ovarian cancer. Given a weak association, two points were mentioned that could have better defined the association, use of hospital-gynecologic disease controls and more information on general population talc use.

Pertaining to finding talc in cancerous tissue, only one histopathologic study has reported the presence of talc in ovarian cancer tissue and the results of this study were questioned because of methodological problems. To clarify this issue, it was recommended that future examination of surgically removed cancerous ovarian tissue should include a search for evidence of talc in the tissue by both histological and mineralogical techniques.

Even though there is a weak epidemiologic association for talc and ovarian cancer, the sequence of events leading from perineal talc exposure to ovarian cancer is at present unclear. It is not known how/if talc particles migrate to ovarian tissue. Conclusive evidence for the presence of talc in ovarian tissue is lacking and if talc reaches ovarian tissue no mechanism for talc carcinogenesis has been defined. Hence, the biologic plausibility to support the statement that talc exposure results in ovarian cancer requires additional evaluation.

February 4, 1994

Talc: Consumer Uses and Health Perspectives

Summary:

Talc Inhalation Studies
Talc: hydrous magnesium silicate; 900,000 tons/year used in the US; 48,000 tons/yr (6%) in cosmetics. Treatment of raw talc for cosmetic use results in 90-95% pure talc. Uses: powders, antiperspirants, pill coatings/fillers, foods (chewing gum/anticaking), medical devices (surgical glove/condom coating; Note: no longer used in surgical gloves). Cosmetic uses: antiperspirants, semi-solid matrices (eye shadow), powders. Talc used in powders is 200 mesh and is the only cosmetically used talc which has the potential for being inhaled. This particle size is too large to be respirable however. Most talc particles in powders will be trapped in the nose. Talc and asbestos materials are not formed under the same geologic conditions, therefore careful selection of mining sites results is asbestos-free talc. Estimated human exposure via respiration when using powder during baby diapering: 0.2 - 2 mg/m^3.

NTP study: Requested by NIOSH due to worker exposure. Talc particles smaller than typically used in cosmetic products were used in the NTP study to determine the effects on inhalation. Larger particles would not have made it into the lungs. Two year study; exposure levels tested in chronic study: 6, 18 mg/m^3. Rodent exposure 2,000 - 20,000 times greater than estimated human exposure. Tumors formed only in female rats at the highest dose. The species of female rats used are known to be particularly sensitive to particulates. No tumors were observed in male or female mice. Adrenal medulla neoplasms were also observed in rats; origin is unknown. Talc exposure tested at the highest level was an "overload"; clearance time from the lung at this concentration is greatly increased. The smaller the particles the longer the clearance time. In a related study, there was no evidence for increased incidence of lung tumors in coal mine workers exposed to coal dust whose estimated exposure was greater than the exposure to particles in the talc rat study. TiO_2, chromium dioxide, volcanic ash and quartz dust have all produced tumors in female rats (not male rats), by inhalation. A negative dust control was not included in the NTP study which raises the question: did the observed tumors result from talc or would they have arisen from any particulate? There was one member of the NTP review panel who did not agree with the conclusions prepared by the study team. This person's comments included: (1) the maximum tolerated dose was exceeded at 18 mg/m^3, and was therefore inappropriate; (2) there was an increase in tumors in the controls over that observed historically for this animal which was neglected in the study conclusions. Historically, talc has been used as the negative control for inhalation studies on silica and asbestos.

Caution was urged when extrapolating the rodent study results to man. Lung branching between rodents and man is different and this will effect which cells are exposed to particulates.

Ovarian Cancer and Talc Use

US annual incidence of ovarian cancer: 15 per 100,000; 8 per 100,000 deaths per year. Trends in mortality and incidence of ovarian cancer have been stable for 20 years. Factors which decrease incidence: use of oral contraceptives, breast feeding, child bearing, hysterectomy. (ie. Activities which reduce the number of times the ovary has to repair itself following release of an egg).

Talc can migrate to the ovaries, though the route is presently unknown. There is some evidence that particulates can migrate to other body tissues via the vascular system. Intestinal absorption is negligible. Radiolabeled talc injected vaginally into rabbits did not migrate to the ovaries.

Questions about talc migration to ovaries originated with a study published by Henderson in 1971 in which talc was found in human ovaries. The study was repeated in 1979 and talc was again found, this time in the ovaries of nontumoragenic women. These studies may have been flawed. Controls may not have been adequately conducted. In another experiment, labeled talc was deposited in the vagina but no translocation to the ovaries was detected. Analytical techniques used by Henderson to determine talc were questioned. Since many minerals are structurally similar, misidentification was likely. Only in the last ten years have methods become available for reliable talc measurement. Mineralogical methods were used to measure talc particulates and not histological techniques. Ovary tissues may have been removed by physicians using gloves contaminated with talc (though in the second study, ovarian tissue was removed with forceps only). Talc granulomas following surgery due to talc on gloves has been reported, but no granulomas were reported in Henderson's studies, raising questions about what particulates Henderson actually observed.

There have been 9 epidemiological studies of the relationship between talc use and ovarian cancer. Two studies showed a statistically significant increase in cancer incidence, the other studies showed a negative correlation. The risk of ovarian cancer prior to 1960 was greater than after 1960. This could be due to the reduction of asbestos fibers in talc due to modern processing techniques. Epidemiological studies suggest a small risk of ovarian cancer for talc users: 1.3 relative risk where 1.0 is equivalent to no risk. There are a number of confounders which will influence epidemiological studies including race, marital status, age, education, history of tubal ligation, use of oral contraceptives, and asbestos exposure. Inherent bias of epidemiological studies were also mentioned including inaccurate

interview information (eg. recollection).

A six fold increase in ovarian cancer has been identified between women in the U.S. and Japan. This may be attributed to dietary fat intake.

General Conclusion: Additional information is needed to make a definitive conclusion about talc use and ovarian cancer. Presently the increased risk of ovarian cancer due to talc exposure is a hypothesis which remains to be tested.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

JAN 25 1994

NOTE TO: William E. Gilbertson, Ph.D.

Subject: Use of talc and magnesium silicate as (1) food ingredients and (2) color additives for use in drug and cosmetic products

As requested, below is a summary for your use in preparation for the 1/31/94 ISRTP Workshop on Talc.

(1) FOOD INGREDIENT USE

Talc - Direct Food Use

Currently, there are no listings in the Code of Federal Regulations (CFR) for the direct use of talc in food. However, the agency has by letter offered the opinion that the use of talc in chewing gum bases would be considered generally recognized as safe (GRAS). Also, the agency has recognized a 1907 Food Inspection Decision that talc may be used in the coating of milled rice. In the latter situations, talc functions as a lubricant and release agent. The agency regards food grade talc as that product meeting the specifications of the Food Chemicals Codex, 3rd edition (FCC). (Attachment 1)

The agency has in preparation a Federal Register proposal to formally recognize the GRAS status of the latter uses of talc.

Talc - Indirect Food Use

Talc has a number of CFR listings for use in packaging materials, coatings, resins, etc. in which it acts as a colorant (producing opacity) or a filler. Talc for these uses must also meet the requirements for food grade material as defined in the Food Chemicals Codex.

21 CFR 182.70	Substances migrating from cotton and cotton fabrics used in dry food packaging
21 CFR 182.90	Substances migrating to food from paper and paperboard products
21 CFR 175.300	Resinous and polymeric coatings

NOTE TO: William E. Gilbertson, Ph.D.

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21 CFR 182.70 Substances migrating from cotton and cotton fabrics used in dry food packaging

21 CFR 182.90 Substances migrating to food from paper and paperboard products

21 CFR 175.300 Resinous and polymeric coatings

21 CFR 175.380	Xylene-formaldehyde resins condensed with 4,4'-isopropylidenediphenol-epichlorohydrin epoxy resins
21 CFR 175.390	Zinc-silicon dioxide matrix coatings
21 CFR 176.170	Components of paper and paperboard in contact with aqueous and fatty food
21 CFR 177.1210	Closures with sealing gaskets for food containers
21 CFR 177.1350	Ethylene-vinyl acetate copolymers
21 CFR 177.1460	Melamine-formaldehyde resins in molded articles
21 CFR 178.3297	Colorants for polymers

The above listings for indirect use frequently include "magnesium silicate" interchangeably with "talc". In reality, talc is a naturally occurring hydrated form of magnesium silicate; while magnesium silicate per se occurs in mineral form, it may also be prepared synthetically. Both Chemical Abstracts and the Food Chemicals Codex recognize the two as separate chemical entities, and the latter provides a monograph for what the agency regards as food grade material. (Attachment 2)

Magnesium silicate - Direct food use

Magnesium silicate is used in food primarily as an anticaking agent and adsorbent material.

There are four CFR listings for use of magnesium silicate as an anticaking agent - three for human food and one for animal feed.

21 CFR 182.2437	Magnesium silicate - GRAS; use in table salt at levels up to 2 %
21 CFR 169.179	Vanilla powder - (Food standard)
21 CFR 169.182	Vanilla-vanillin powder - (Food standard) -
21 CFR 582.2437	Magnesium silicate - GRAS; animal feed

The agency has also by letter offered the opinion that magnesium silicate (synthetic magnesium silicate) meeting the specifications of Food Chemical Codex may be used for certain other direct and indirect uses. In particular, magnesium silicate may be used as a filter aid to remove impurities from cooking oil.

21 CFR 175.380	Xylene-formaldehyde resins condensed with 4,4'-isopropylidenediphenol-epichlorohydrin epoxy resins
21 CFR 176.350	Zinc silicon dioxide matrix coatings
21 CFR 176.170	Components of paper and paperboard in contact with aqueous and fatty food
21 CFR 177.1210	Closures with sealing gaskets for food containers
21 CFR 177.1350	Ethylene-vinyl acetate copolymers
21 CFR 177.1460	Melamine-formaldehyde resins in molded articles
21 CFR 178.3297	Colorants for polymers

The above listings for indirect use frequently include "magnesium silicate" interchangeably with "talc". In reality, talc is a naturally occurring hydrated form of magnesium silicate; while magnesium silicate per se is rare in mineral form, it may also be prepared synthetically. Both Chemical Abstracts and the Food Chemicals Codex recognize the two as separate chemical entities, and the latter provides a monograph for which the agency regards as food grade material. (Attachment 2)

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(2) COLOR ADDITIVE USE OF TALC FOR DRUG AND COSMETIC PRODUCTS

Talc may be used as a color additive in drugs generally and as a substratum for certain drug and cosmetic color additive lakes (lakes are subject to batch certification by the agency). The United States Pharmacopeia (USP) serves as a basis for appropriate specifications for talc in these uses.

21 CFR 73.1550 Talc (Attachment 3)

21 CFR 82.1051 Lakes (D&C) (Attachment 4)

21 CFR 82.2051 Lakes (Ext. D&C)

As a further note, magnesium silicate is not listed for use as a color additive.

Please feel free to call me if you have any questions, or if I can assist you further.

Kitty

Catherine J. Bailey

Revised 1-27-94

January 27, 1994

Note To : John E. Bailey, Ph.D. (HFS-100)
Director
Office of Cosmetics and Colors

From : Stanley R. Milstein, Ph.D. (HFS-101) SRM
Special Assistant to the Director
Office of Cosmetics and Colors (OCAC)

Subject : **TALC SYMPOSIUM - SUGGESTED COSMETIC COMMENTS**

This note provides you with suggested comments for Dr. Gilbertson's ISRTP Workshop presentation on Talc, dealing with cosmetic perspectives.

Background

Talc, a complex hydrated magnesium silicate mineral, has been mined since the time of the ancient Greeks (Hildick-Smith) and has a history of being mined in several regions of the world, including Europe (esp. France and Italy), the Orient (including Manchuria and Japan), India, and the United States (including California, Montana, North Carolina, and Alabama). The cosmetic literature reports (whether accurately or not) that Italian cosmetic talc has been the western world's standard for centuries (Mulryan).

According to a now-dated U.S. Bureau of Mines estimate from 1979, the world's talc industry produced nearly 6.9 million tons of talc per year with a market value of ca. $ 435,000,000 (Kirk-Othmer). Of this total, ca. 17% of which could be expected to be of cosmetic quality (Mulryan).

Because cosmetic and pharmaceutical (OTC) product matrices that employ cosmetic talc are also expected to possess desirable aesthetic characteristics that will find widespread consumer acceptance, high quality cosmetic talcs...regardless of their geographic source, share three (3) common characteristics: high chemical purity, a clean white color, and good "slip", in addition to "softness" (Mohs Mineralogical Scale grade of 1) and acceptable texture. It has been said that a good quality talc should have such particle fineness that 98% of it goes through a standard 200-mesh sieve (i.e., 98% of the particles are sized < 74 microns); however, ultrafine grades of talc can also be produced and micronized talcs having particle sizes of only a few microns are also commercially available (Martin).

Uses of Talc

Talc is used in cosmetic products for the special "feel", "shine" and appearance (esp. "transparency" in face powders) that it imparts to the cosmetic formulation. A good talc should adhere to the skin evenly and aid in concealing superficial skin imperfections. Because of its softness and slip (lubricity), the

talc may also have an emollient effect on the skin, resisting mechanical abrasion and chafing of the skin, due to the rubbing of skin-skin or clothing-skin. The surface area of a talc also affects its ability to reflect light incident on the skin and, therefore, may also relate to its ability to reduce the perceived intensity or tint of a colorant. Chemically surface-treated ultra fine talcs can also afford water resistance in a cosmetic or OTC formulation.

Under the Federal Food Drug and Cosmetic Act (FDCA) of 1938, there is no requirement for premarket approval of cosmetics or, with the exception of color additives and a short "negative list" of prohibited substances given at 21 CFR 700, their constituent raw materials. Because there is no mandatory reporting requirement, FDA does not know exactly how many products are on the market that contain talc as an ingredient. However, FDA does maintain a Voluntary Registration Program (CVRP) for cosmetics (c.f., 21 CFR 720), in which companies can report their finished products and qualitative disclosures of ingredient composition.

The current CVRP database indicates that there are about 2000 products in some 45 different cosmetic product categories that are voluntarily registered with FDA. A few examples may be illustrative. There are only 7 products registered as "baby products" (baby lotions/ oils/ powders/ and creams), while under the more generic "powders" category, we find 425 products (21%) registered. More still are registered under the heading of "blushers, face powders, and foundations" where we find an additional 665 products (33.2%). Finally, there are 9 "men's talcum products" and 35 "foot powders".

It should be emphasized that this is not an exhaustive recounting of all cosmetic products or even of all product categories known to utilize talc. Nor does it represent the total universe of products or manufacturers of talc-containing cosmetic products in the industry. It is likely, however, that these registrations represent a significant portion of the volume of cosmetic products utilizing talc and distributed in the United States.

Based upon the figures given, as one surveys the product categories in which talc has been reported to be used, it seems clear that a significant number of cosmetic products are marketed at present for which there is a clear possibility of inhalation or perineal exposure.

Talc - Chemistry and Specifications

Talc has been described rather poetically as resulting "... during intense geologic upheavals underground, (which cause) torrents of magnesia-rich hot waters (to alter) basic rocks to hydrous magnesium silicate..." (Mulryan). The type of parent rock and the degree of alteration determine the purity and particle structure

of the talc. According to the CTFA specification for cosmetic talc, the balance of the talc may consist of other naturally occuring minerals such as calcite, chlorite, dolomite, kaolin, and magnesite.

Prior to the early 1970's, there was some concern that talc mined and processed commercially could be contaminated by asbestos or asbestiform minerals. Since that time, however, the cosmetic industry specification for talc has been tightened to virtually eliminate that concern. For example, a 1977 investigation of 46 talc samples by FDA revealed only 3 to contain asbestos (tremolite or anthophyllite), and even then the level was only 0.1% or less.

As mentioned earlier, there are no premarket approval requirements under FDCA for cosmetics or their constituent raw materials. Accordingly, there are no FDA-mandated regulatory standards or specifications for the grade of talc that may be used in formulating cosmetic products. However, the Agency did note in its discussion concerning talc as a Category I skin protectant ingredient for the prevention of diaper rash (c.f., 55 FR 25224, June 20, 1990) that:

"....cosmetic talc should contain at least 90% platy talc (having flat as opposed to fibrous particles) that is free of detectable amounts of fibrous minerals, including asbestos...".

Other general talc specifications have been published by the U.S. Pharmacopoeia, which specifies impurity limits, and by the CTFA (Cosmetic, Toiletry, and Fragrance Association), which now also dictates that there should be no detectable fibrous amphiboles such as asbestiform tremolite. (OSHA defines 'fibers' as particles of the relevant minerals which are 5 micometers or longer and having an aspect ratio of at least 3:1; c.f., 57 FR 24315, June 8, 1992). There is also a Food Chemicals Codex (FCC) talc specification, but the Agency has no way of knowing whether any given company in the cosmetic industry employs talc conforming to the USP, CTFA, or FCC specification. Parenthetically, we might note that ASTM has also published a talc standard for paints (Standard D-605-69).

Acute and Chronic Medical Consequences of Talc Use

The literature records that some pediatric authorities have recommended that the use of talcum powder (one of whose main constituents is talc) should be discouraged on neonates due to the possibility of acute massive inhalation-associated infant death. Some recent epidemiological studies, which have generated considerable public interest, have suggested an association between chronic female perineal talc dusting and the subsequent development of ovarian cancer. Also, there have been occasional occupational reports of chronic inhalation of talc dusts associated with the subsequent development of pulmonary fibrosis.

It is beyond the scope of this presentation to do more than take note of these medical and/or occupational consequences, alleged or proven, that may be associated with talc usage, and which have come to FDA's attention as well as to the attention of the American Public. We look forward to the full and authoritative discussion of these issues and others which will take place at this Symposium.

I recognize that there may be aspects of these comments that Dr. Gilbertson may wish to avoid as an FDA spokesperson, but I believe that there is enough given herein under the heading of "cosmetic perspectives" to allow for some judicious editing, as you may think best.

SRMilstein

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-(1-methylpropyl)-5-(2-propenyl)-.
5-Allyl-5-*sec*-butylbarbituric acid [*115-44-6*].

» Talbutal contains not less than 98.0 percent and not more than 102.0 percent of $C_{11}H_{16}N_2O_3$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Talbutal Reference Standard*—Dry in vacuum at 60° for 4 hours before using.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, previously dried, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Talbutal RS.

B: The ultraviolet absorption spectrum of a 1 in 67,000 solution in pH 9.6 alkaline borate buffer (see under *Solutions* in the section, *Reagents, Indicators, and Solutions*) exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Talbutal RS, concomitantly measured, and the respective absorptivities, calculated on the dried basis, at the wavelength of maximum absorbance at about 241 nm do not differ by more than 3.0%.

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 4 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Assay—Transfer about 500 mg of Talbutal, accurately weighed, to a 125-mL conical flask, and dissolve in 25 mL of dimethylformamide. Add 5 drops of a freshly prepared 1 in 1000 solution of azo violet in dimethylformamide, and titrate with 0.1 *N* lithium methoxide VS to a blue-violet end-point, taking precautions against the absorption of atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *N* lithium methoxide is equivalent to 22.43 mg of $C_{11}H_{16}N_2O_3$.

Talbutal Tablets

» Talbutal Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_{16}N_2O_3$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Talbutal Reference Standard*—Dry in vacuum at 60° for 4 hours before using.

Identification—Shake a quantity of finely powdered Tablets, equivalent to about 200 mg of talbutal, with 10 mL of pentane for 5 minutes, and filter through a medium-porosity, sintered-glass filter. Discard the filtrate, and shake the residue with 10 mL of chloroform for 15 minutes. Filter through the same filter, evaporate the filtrate with the aid of gentle heat to dryness, and use the residue of talbutal so obtained for the following tests.

A: A portion of the residue responds to *Identification test A* under *Talbutal*.

B: To the remainder of the residue add 1 mL of glacial acetic acid and 10 mL of water, mix, then add bromine TS dropwise: the bromine color is discharged on shaking.

Dissolution ⟨711⟩—

Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Time: 45 minutes.

Procedure—Determine the amount of $C_{11}H_{16}N_2O_3$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 241 nm of filtered portions of the solution under test, suitably diluted with pH 9.6 alkaline borate buffer (see under *Buffer Solutions* in the section, *Reagents, Indicators, and Solutions*), in comparison with a Standard solution having a known concentration of USP Talbutal RS in the same medium.

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_{11}H_{16}N_2O_3$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Standard preparation—Dissolve an accurately weighed quantity of USP Talbutal RS in 5 mL of alcohol contained in a 100-mL volumetric flask, dilute with pH 9.6 alkaline borate buffer (see under *Solutions* in the section, *Reagents, Indicators, and Solutions*) to volume, mix, and dilute quantitatively and stepwise with the same alcohol-buffer mixture to obtain a solution having a known concentration of about 10 µg per mL.

Assay preparation—Weigh and finely powder not less than 20 Talbutal Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg of talbutal, to a separator with the aid of 15 mL of water, and add 5 mL of 3 *N* hydrochloric acid. Extract with four 25-mL portions of chloroform, filter each portion through chloroform-washed cotton into a 250-mL volumetric flask, dilute with chloroform to volume, and mix. Transfer 5.0 mL of this solution to a beaker, and evaporate just to dryness. Transfer the residue to a 100-mL volumetric flask with the aid of, first, 5 mL of alcohol, and then pH 9.6 alkaline borate buffer. Dilute with the buffer to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* in 1-cm cells at the wavelength of maximum absorbance at about 241 nm, with a suitable spectrophotometer, using a 1 in 20 solution of alcohol in pH 9.6 alkaline borate buffer as the blank. Calculate the quantity, in mg, of $C_{11}H_{16}N_2O_3$ in the portion of Tablets taken by the formula:

$$5C(A_U/A_S),$$

in which C is the concentration, in µg per mL, of USP Talbutal RS in the *Standard preparation*, and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation*, respectively.

Talc

» Talc is a native, hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate.

Packaging and storage—Preserve in well-closed containers.

Identification—Mix about 200 mg of anhydrous sodium carbonate with 2 g of anhydrous potassium carbonate, and melt in a platinum crucible. To the melt add 100 mg of the substance under test, and continue heating until fusion is complete. Cool, and transfer the fused mixture to a dish or beaker with the aid of about 50 mL of hot water. Add hydrochloric acid to the liquid until effervescence ceases, then add 10 mL more of the acid, and evaporate the mixture on a steam bath to dryness. Cool, add 20 mL of water, boil, and filter the mixture: an insoluble residue of silica remains. Dissolve in the filtrate about 2 g of ammonium chloride, and add 5 mL of 6 *N* ammonium hydroxide. Filter, if necessary, and add dibasic sodium phosphate TS to the filtrate: a white, crystalline precipitate of magnesium ammonium phosphate separates.

Microbial limit—The total bacterial count does not exceed 500 per g.

Loss on ignition ⟨733⟩—Weigh accurately about 1 g, and ignite at 1000° to constant weight: it loses not more than 6.5% of its weight.

Acid-soluble substances—Digest 1.00 g with 20 mL of 3 *N* hydrochloric acid at 50° for 15 minutes, add water to restore the original volume, mix, and filter. To 10 mL of the filtrate add 1 mL of 2 *N* sulfuric acid, evaporate to dryness, and ignite to constant weight: the weight of the residue does not exceed 10 mg (2.0%).

Reaction and soluble substances—Boil 10 g with 50 mL of water for 30 minutes, adding water from time to time to maintain approximately the original volume, and filter: the filtrate is neutral to litmus paper. Evaporate one-half of the filtrate to dryness, and dry at 105° for 1 hour: the weight of the residue does not exceed 5 mg (0.1%).

Water-soluble iron—Slightly acidify with hydrochloric acid the remaining half of the filtrate obtained in the test for *Reaction*

and soluble substances, and add 1 mL of potassium ferrocyanide TS: the liquid does not acquire a blue color.

Arsenic, Heavy metals, and Lead—

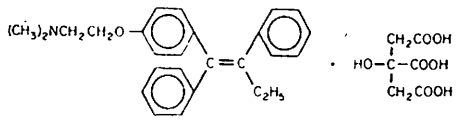
Test solution—Transfer 10.0 g to a 250-mL flask, and add 50 mL of 0.5 *N* hydrochloric acid. Attach a reflux condenser to the flask, heat on a steam bath for 30 minutes, cool, transfer the mixture to a beaker, and allow the undissolved material to settle. Decant the supernatant liquid through thick, strong, medium-speed filter paper into a 100-mL volumetric flask, retaining as much as possible of the insoluble material in the beaker. Wash the slurry and beaker with three 10-mL portions of hot water, decanting each washing through the filter into the flask. Finally, wash the filter paper with 15 mL of hot water, cool the filtrate to room temperature, dilute with water to volume, and mix. Use this *Test solution* for the following tests.

Arsenic, Method I ⟨211⟩—Use 10 mL of the *Test solution* in preparing the *Test Preparation*. The limit is 3 ppm.

Heavy metals ⟨231⟩—Use 5 mL of the *Test solution* in preparing the *Test Preparation*. The limit is 0.004%.

Lead ⟨251⟩—A 5-mL portion of the *Test solution* contains not more than 5 µg of lead (0.001%).

Tamoxifen Citrate



$C_{26}H_{29}NO.C_6H_8O_7$ 563.65

Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethyl-, (*Z*)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

(*Z*)-2-[*p*-(1,2-Diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethylamine citrate (1:1) [*54965-24-1*].

» Tamoxifen Citrate contains not less than 99.0 percent and not more than 101.0 percent of $C_{26}H_{29}NO.C_6H_8O_7$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Reference standard—*USP Tamoxifen Citrate Reference Standard*—Dry at 105° for 4 hours before using.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it exhibits maxima only at the same wavelengths as that of a similar preparation of USP Tamoxifen Citrate RS, exhibiting a single band in the 1700 to 1740 cm^{-1} region of the spectrum.

B: The ultraviolet absorption spectrum of a 1 in 50,000 solution in methanol exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Tamoxifen Citrate RS, concomitantly measured.

Melting range ⟨741⟩: melts at about 142°, with decomposition.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%.

***E*-isomer**—

Mobile phase—Prepare a methanol solution containing, in each liter, 320 mL of water, 2 mL of glacial acetic acid, and 1.08 g of sodium 1-octanesulfonate.

Standard preparation—Dissolve a suitable quantity, accurately weighed, of USP Tamoxifen Citrate RS in *Mobile phase* to obtain a solution having a known concentration of about 600 µg per mL.

Test preparation—Using about 30 mg of Tamoxifen Citrate, accurately weighed, proceed as directed under *Standard preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4-mm × 30-cm column that contains packing L11. The flow rate is about 0.7 mL per minute. Chromatograph five replicate injections of the *Standard preparation*, and record the respo... of the major peak: the relative standard deviation is not m... than 3.0% and the relative retention time of the minor *E*-iso... peak to that of the *Z*-isomer peak is not greater than 0.93...

Procedure—Separately introduce equal volumes (about 20... of the *Test preparation* and the *Standard preparation* into... liquid chromatograph by means of a suitable sampling v... Measure the minor peak responses for the *E*-isomer obtained f... the *Standard preparation* and the *Assay preparation*. Calcu... the quantity, in mg, of *E*-isomer ($C_{26}H_{29}NO.C_6H_8O_7$) in... portion of Tamoxifen Citrate taken by the formula:

$$0.05C(r_U/r_S),$$

in which C is the concentration, in µg per mL, of the *E*-iso... as the citrate, based on its declared content in USP Tamox... Citrate RS in the *Standard preparation*, and the r_U and r_S... the minor peak responses obtained from the *Assay prepara...* and the *Standard preparation*, respectively. The *E*-isomer... tent is not more than 1.0% of tamoxifen citrate ($C_{26}H_{29}N...$ $C_6H_8O_7$).

Related impurities—

Test preparation A—Disperse about 3 g in 100 mL of w... in a separator. Over a 10-minute period add 50 mL of 0... sodium hydroxide, with mixing. Extract with two 50-mL port... of ether, and combine the extracts. Wash with 20 mL of wa... remove the water layer, and dry the ether layer over anhyd... sodium sulfate. Evaporate the ether layer under nitrogen, a... dry in vacuum at room temperature for 2 hours. Accurat... weigh 1.5 g of the residue into a 10-mL volumetric flask, a... 5.0 mL of a mixture of 5 volumes of acetic anhydride and... volumes of pyridine, and heat at 60° for 10 to 15 minutes. Co... dilute with the same solvent mixture to volume, and mix.

Test preparation B—Using the same acetic anhydride–py... dine mixture, prepare a 1:200 dilution of *Test preparation A*.

Chromatographic system (see *Chromatography* ⟨621⟩)—Th... ically, the gas chromatograph is equipped with a flame-ioniza... detector, and contains a 1-m × 4-mm glass column packed w... 5 percent liquid phase G17 on 100- to 120-mesh support S1... conditioned at 300° for 24 hours. The column and injection po... are maintained at about 260° and the detector at about 30... Dry helium is used as the carrier gas at a flow rate of about... mL per minute. In a suitable chromatogram, five replicate in... jections of *Test preparation B* show a relative standard deviati... of not more than 3.0%.

Procedure—Inject equal portions (about 2 µL), accurat... measured, of *Test preparation A* and *Test preparation B*... the chromatograph, and record the chromatograms from 0.1... 5.0 relative to the retention time of the major peak. Measure... individual areas of the peaks other than those produced by... solvent and the tamoxifen on the chromatograms obtained fro... *Test preparation A*, and calculate their sum. No single peak ar... is greater than total area of the tamoxifen peak on the chr... matogram obtained from *Test preparation B* (0.5%), and the su... of the peak areas is not greater than twice the total area of... tamoxifen peak on the chromatogram obtained from *Test pr... aration B* (1.0%).

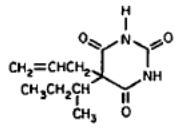
Iron ⟨241⟩—Accurately weigh 1.0 g, and transfer to a suit... crucible. Add sufficient sulfuric acid to wet the substance, a... carefully ignite at a low temperature until thoroughly char... (The crucible may be loosely covered with a suitable lid duri... the charring.) Add to the carbonized mass 2 mL of nitric a... and 5 drops of sulfuric acid, and heat cautiously until white fum... no longer are evolved. Ignite, preferably in a muffle furnace... 500° to 600°, until the carbon is completely burned off. Co... add 10 mL of warm 0.1 *N* hydrochloric acid, and digest for ab... 5 minutes. Transfer the contents of the crucible with the aid... small portions of water to a 50-mL volumetric flask, dilute wi... water to volume, and mix. Pipet 10 mL from the volumetric fl... into a color-comparison tube, dilute with water to 45 mL, a... mL of hydrochloric acid, and mix. The limit is 0.005%.

Arsenic, *Method II* ⟨211⟩—Use 10 mL of dilute sulfuric ac... in 2) instead of 5 mL of sulfuric acid. The limit is 2 ppm.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Assay—Weigh accurately about 1 g of Tamoxifen Citrate, d... dissolve in 150 mL of glacial acetic acid. Titrate the solut... with 0.1 *N* perchloric acid VS, determining the end-point p...

Talbutal



$C_{11}H_{16}N_2O_3$ 224.26

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-(1-methylpropyl)-5-(2-propenyl)-.

5-Allyl-5-*sec*-butylbarbituric acid [*115-44-6*].

» Talbutal contains not less than 98.0 percent and not more than 102.0 percent of $C_{11}H_{16}N_2O_3$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Talbutal Reference Standard*—Dry in vacuum at 60° for 4 hours before using.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, previously dried, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Talbutal RS.

B: The ultraviolet absorption spectrum of a 1 in 67,000 solution in pH 9.6 alkaline borate buffer (see under *Solutions*, in the section, *Reagents, Indicators, and Solutions*) exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Talbutal RS, concomitantly measured, and the respective absorptivities, calculated on the dried basis, at the wavelength of maximum absorbance at about 241 nm do not differ by more than 3.0%.

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 4 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Assay—Transfer about 500 mg of Talbutal, accurately weighed, to a 125-ml conical flask, and dissolve in 25 ml of dimethylformamide. Add 5 drops of a freshly prepared 1 in 1000 solution of azo violet in dimethylformamide, and titrate with 0.1 *N* lithium methoxide VS to a blue-violet end-point, taking precautions against the absorption of atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each ml of 0.1 *N* lithium methoxide is equivalent to 22.43 mg of $C_{11}H_{16}N_2O_3$.

Talbutal Tablets

» Talbutal Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_{16}N_2O_3$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Talbutal Reference Standard*—Dry in vacuum at 60° for 4 hours before using.

Identification—Shake a quantity of finely powdered Tablets, equivalent to about 200 mg of talbutal, with 10 ml of pentane for 5 minutes, and filter through a medium-porosity, sintered-glass filter. Discard the filtrate, and shake the residue with 10 ml of chloroform for 15 minutes. Filter through the same filter, evaporate the filtrate with the aid of gentle heat to dryness, and use the residue of talbutal so obtained for the following tests.

A: A portion of the residue responds to *Identification test A* under *Talbutal*.

B: To the remainder of the residue add 1 ml of glacial acetic acid and 10 ml of water, mix, then add bromine TS dropwise: the bromine color is discharged on shaking.

Disintegration ⟨701⟩: 30 minutes.

Weight variation ⟨931⟩: meet the requirements for *Tablets*.

Assay—

Standard preparation—Dissolve an accurately weighed quantity of USP Talbutal RS in 5 ml of alcohol contained in a 100-ml volumetric flask, dilute with pH 9.6 alkaline borate buffer (see under *Solutions*, in the section, *Reagents, Indicators, and Solutions*) to volume, mix, and dilute quantitatively and stepwise with the same alcohol-buffer mixture to obtain a solution having a known concentration of about 10 µg per ml.

Assay preparation—Weigh and finely powder not less than 20 Talbutal Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg of talbutal, to a separator with the aid of 15 ml of water, and add 5 ml of 3 *N* hydrochloric acid. Extract with four 25-ml portions of chloroform, filter each portion through chloroform-washed cotton into a 250-ml volumetric flask, dilute with chloroform to volume, and mix. Transfer 5.0 ml of this solution to a beaker, and evaporate just to dryness. Transfer the residue to a 100-ml volumetric flask with the aid of, first, 5 ml of alcohol, and then pH 9.6 alkaline borate buffer. Dilute with the buffer to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* in 1-cm cells at the wavelength of maximum absorbance at about 241 nm, with a suitable spectrophotometer, using a 1 in 20 solution of alcohol in pH 9.6 alkaline borate buffer as the blank. Calculate the quantity, in mg, of $C_{11}H_{16}N_2O_3$ in the portion of the Tablets taken by the formula: $5C(A_U/A_S)$, in which C is the concentration, in µg per ml, of USP Talbutal RS in the *Standard preparation*, and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation*, respectively.

Talc

» Talc is a native, hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate.

Packaging and storage—Preserve in well-closed containers.

Identification—Mix 500 mg with about 200 mg of anhydrous sodium carbonate and 2 g of anhydrous potassium carbonate, and heat the mixture in a platinum crucible until fusion is complete. Cool, and transfer the fused mixture to a dish or beaker with the aid of about 50 ml of hot water. Add hydrochloric acid to the liquid until effervescence ceases, then add 10 ml more of the acid, and evaporate the mixture on a steam bath to dryness. Cool, add 20 ml of water, boil, and filter the mixture: an insoluble residue of silica remains. Dissolve in the filtrate about 2 g of ammonium chloride, and add 5 ml of 6 *N* ammonium hydroxide. Filter if necessary, and add sodium phosphate TS to the filtrate: a white, crystalline precipitate of magnesium ammonium phosphate separates.

Loss on ignition—Weigh accurately about 1 g, and ignite at red heat to constant weight: it loses not more than 5.0% of its weight.

Acid-soluble substances—Digest 1.00 g with 20 ml of 3 *N* hydrochloric acid at 50° for 15 minutes, add water to restore the original volume, mix, and filter. To 10 ml of the filtrate add 1 ml of 2 *N* sulfuric acid, evaporate to dryness, and ignite to constant weight: the weight of the residue does not exceed 10 mg (2.0%).

Reaction and soluble substances—Boil 10 g with 50 ml of water for 30 minutes, adding water from time to time to maintain approximately the original volume, and filter. The filtrate is neutral to litmus paper. Evaporate one-half of the filtrate to dryness, and dry at 105° for 1 hour: the weight of the residue does not exceed 5 mg (0.1%).

Water-soluble iron—Slightly acidify with hydrochloric acid the remaining half of the filtrate obtained in the test for *Reaction and soluble substances*, and add 1 ml of potassium ferrocyanide TS: the liquid does not acquire a blue color.

Adhesive Tape

» Adhesive Tape consists of fabric and/or film evenly coated on one side with a pressure-sensitive, adhesive mixture. Its length is not less than 98.0 percent of that declared on the label, and its average width is not less than 95.0 percent of the declared width. If Adhesive Tape has been rendered sterile, it is protected from contamination by appropriate packaging.

Packaging and storage—Preserve in well-closed containers, and

8/14/23

Dennis
Havern
Kornhauser
Bronaugh
Tollefson
Lorentzen

C·T·F·A

Representing the personal care products industry

E. Edward Kavanaugh
President

April 5, 1993

John Bailey, Ph.D. (HFF-440)
Acting Director, Office of
Cosmetics and Colors
Food and Drug Administration
200 C Street, S.W.
Washington, D.C. 20204

Dear John:

Enclosed is a paper reporting on a study evaluating the ability of three talc samples to induce enhanced unscheduled DNA synthesis (UDS), or sister chromatid exchanges (SCEs) (Endo-Capron, et. al., *In-Vitro Response of Rat Pleural Mesothelial Cells to Talc Samples in Genotoxicity Assays (Sister Chromatid Exchanges and DNA Repair)*. Toxic. In-Vitro. 7(1) 7-14. 1993). Effects observed were compared with those obtained using negative controls (attapulgite and anatase) and positive controls (chrysotile and crocidolite asbestos). The authors speculate that fiber size and shape may be of significance.

This paper would tend to support the concern raised by Dr. Osterberg and others that the results of the NTP study reported in 1992 were caused by an overload of the lung clearance mechanism, rather than any direct genotoxicity of the talc used in the experiment. I would appreciate it if you would include a copy of this paper in the information for review by FDA toxicologists interested in the potential hazards from inhalation from talc.

Best Regards,

Jerry

G.N. McEwen, Jr., Ph.D., J.D.
Vice President - Science

GNM/pcl
cc: Talc Interested Party Task Force
Scientific Advisory Executive Committee

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IN VITRO RESPONSE OF RAT PLEURAL MESOTHELIAL CELLS TO TALC SAMPLES IN GENOTOXICITY ASSAYS (SISTER CHROMATID EXCHANGES AND DNA REPAIR)

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*INSERM-U139, Laboratoire de Toxicologie Cellulaire et Moléculaire de l'Environnement, CHU Henri Mondor, 94010 Créteil and †Laboratoire d'Etude des Particules Inhalées, DASS, 11 rue Georges Eastmann, 75013 Paris, France

(Received 16 April 1992; revisions received 11 August 1992)

Abstract—The genotoxicity of three samples of talc has been determined using *in vitro* cell systems previously developed for testing asbestos fibres. The talc samples used consisted of particles of respirable size in order to test the effect of particles likely to be deposited in the lung. Genotoxicity was tested in cultures of rat pleural mesothelial cells (RPMC) using genotoxicity assays for unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs). The effects were compared with those obtained with negative controls (attapulgite and anatase) and positive controls (chrysotile and crocidolite asbestos). In contrast to asbestos, none of the talc samples, nor the negative controls, induced enhancement of UDS or SCEs in treated cultures in comparison with the untreated cultures.

INTRODUCTION

Talc is a mineral commonly used in various industries including the ceramics, paper, plastics, paints, pharmaceutical and cosmetics industries. It is a magnesium silicate of similar chemical composition to chrysotile asbestos fibres but with a different structure. IARC has evaluated the biological effects of talc (IARC Working Group, 1987); according to their findings the results obtained in previous experiments *in vivo* and *in vitro* were inadequate to evaluate the carcinogenicity or genotoxicity of talc because of the limited number of studies. Data from animal studies did not show an excess of pleural sarcomas or mesotheliomas after the intrapleural administration of talc (Endo-Capron *et al.*, 1990; Stanton *et al.*, 1977; Wagner *et al.*, 1977). From data from epidemiological studies, the IARC Working Group (1987) concluded that it was possible that carcinogenicity could result from exposure to some specific samples found to be associated with fibrous tremolite. However, epidemiological studies have been updated recently and no evidence of increased risk of lung cancer has been found (Weill *et al.*, 1990). Some authors have examined the association between genital talcum powder exposure and ovarian cancer (Harlow and Weiss, 1989); no appreciable altered risk was observed following exposure to baby powders, which are reported to contain only talc, but an increased risk was associated with the use of talc-containing powders, that is, also containing deodorizing substances or a variety of other free and bound silica (Harlow and Weiss, 1989).

The present experiments were designed to determine whether talc particles of respirable dimensions exerted a genotoxic effect on cultures of rat pleural mesothelial cells (RPMC). Pleural mesothelial cells are an important target for fibrous particles inhaled from our environment and can be used as test models to determine the *in vitro* effects of particle matter. In addition, talc has been used to overcome pleural effusion (IARC Working Group, 1987). It is therefore of interest to determine the effects of pure talc on RPMC. In previous experiments, we have used RPMC to study the genotoxicity of asbestos fibres. Enhancement of unscheduled DNA synthesis (UDS; Renier *et al.*, 1990) and sister chromatid exchanges (SCE; Achard *et al.*, 1987) have been observed in cultured RPMC after exposure to chrysotile or crocidolite fibres, but not after exposure to a non-carcinogenic sample of attapulgite. Identical tests were applied in this study in order to determine the effects of pure talc.

MATERIALS AND METHODS

Particles and test compounds. Three samples of European talc provided by Eurotalc (Brussels, Belgium) were studied. One sample each of French talc (no. 7841). Italian talc (no. 5726) and Spanish

‡To whom correspondence should be addressed.
Abbreviations: FCS = foetal calf serum; HU = hydroxyurea; RPMC = (rat pleural mesothelial cells); SCE = sister chromatid exchange; TEM = transmission electron microscopy; UDS = unscheduled DNA synthesis.

90–95% of talc, the other compounds being chlorite and dolomite. Anatase (a gift from P. Sebastien, Cerchar, France) and attapulgite (from Mormoiron, France) were tested as negative reference particles; Rhodesian chrysotile and crocidolite from the Union Internationale Contre le Cancer (UICC) as positive reference particles. The particles were dispersed in culture medium at a concentration of 560 μg/ml by sonication for 5 min (20 KHz, 3 W). Chemicals used as controls, mitomycin C (Choay, Paris, France) and K_2CrO_4 (Aldrich Chemical Co., Milwaukee, MO, USA), were solubilized in water and in culture medium, respectively.

Transmission electron microscopy (TEM). Particles at a concentration of 100 μg/ml were dispersed in culture medium. An aliquot of the suspension was filtered through a 0.40-μM pore size Nuclepore filter. The filters were transferred to electron microscopic grids and dissolved according to the method routinely used in the laboratory (Sébastien *et al.*, 1978). The size of the particles was determined following a systematic scanning of the grid at two magnifications (×33,000 and ×26,000).

Cell culture. Rat pleural mesothelial cells (RPMC) were obtained as described elsewhere (Jaurand *et al.*, 1981). Briefly, primary RPMC cultures were obtained by scraping the parietal pleura and allowing the cells to grow in multiwell tissue culture plates. The cultures were maintained in complete medium (i.e. Ham's F10 medium; Flow Laboratories, Irvine, Ayrshire, Scotland) supplemented with 2 mM-L-glutamine (Flow Laboratories), 1 mM-vitamin C (Sigma Chemical Co., St Louis, MO, USA), 10 mM-HEPES (Seromed, Berlin, Germany), 10% foetal calf serum (FCS; from Boehringer, Mielan, France), 100 U penicillin ml and 50 μg streptomycin ml (both antibiotica from Flow Laboratories). When the cells reached confluence they were subcultured. From passage 5, RPMC were subcultured approximately every week by standard trypsinization and used between passages 5 and 15.

Ultrastructural analysis. 24 hr after plating, talc was added to the RPMC in the tissue culture dishes at a concentration of 10 μg/cm². Electron microscopic studies were carried out according to standard methods previously described (Jaurand *et al.*, 1979). The solid compound concentration was expressed as μg/cm² to take into consideration the particle settling; in these culture conditions, 1 μg/cm² is equivalent to 5 μg/ml.

Unscheduled DNA synthesis (UDS). RPMC were cultured in 24-well cluster dishes (Falcon, France); 8×10^4 cells were plated per well in complete medium. Cells reached confluence after 4 days of incubation. The medium of the confluent culture was replaced with RPMI (Flow Laboratories) containing 1% FCS (Boehringer), 5 mM-hydroxyurea (HU; Sigma) to arrest cells in G1, 100 U penicillin/ml and 50 μg streptomycin/ml (both from Flow Laboratories). The cells were incubated for 24 hr in a humidified atmos- treated for 24 hr with the indicated dose of particles (1 μg/cm² is equivalent to 5 μg/ml) in 1% FCS medium containing 5 mM-HU and [*methyl*-^{3}H] thymidine (Amersham, les Ulis, France) at 4 μCi/ml. The amount of radioactivity incorporated into DNA was determined as described elsewhere (Renier *et al.*, 1990). Six wells were used per treatment. After treatment, cells were washed three times with phosphate buffered saline. Acid-soluble material was removed by rinsing with 10% cold trichloracetic acid for 10 min and incubated in a mixture of 0.2 M-NaOH and 1% sodium dodecyl sulphate. Aliquots of 200 μl were mixed with scintillation fluid (Pico-fluor, Packard) and radioactivity was measured with a Beckman LS 6000SC scintillation counter. Cell DNA content was determined according to West *et al.* (1985) in separate wells treated with the minerals in the same conditions as described above. Results are expressed as dpm/μg DNA. All studies were carried out with coded samples.

Sister chromatid exchanges (SCEs). RPMC were plated at a density of 2×10^6 cells per 75-cm² flask in RPMI medium supplemented with 10% FCS. Cells were treated either with test chemicals or with several concentrations of particles plus 3 μg bromodeoxyuridine/ml 24 hr after the plating of the culture. In these culture conditions, 1 μg/cm² is equivalent to 7.5 μg/ml. The cultures were incubated with the test compound at 37°C for 48 hr in the dark. 2 hr before harvesting cells, colchicine (Sigma) at a final concentration of 0.2 μg/ml was added to each culture. Metaphase cells were then detached with 0.25% trypsin (Eurobio, Paris, France), collected in 15-ml corex tubes and centrifuged at 1500 rpm for 7 min. The supernatant was removed. Cells were treated with 0.075 M-KCl at 37°C for 30 min before fixation in methanol–glacial acetic acid (3:1, v/v). The fixative was changed three times and the last fixation step lasted for one night. The cell suspension was dropped onto an ice-cold slide. Cells were stained by the fluorescence plus Giemsa technique (Perry and Wolff, 1974). 30 metaphases exhibiting 37–42 chromosomes were counted per assay. All studies were carried out with coded samples.

Statistical analysis. The significance of UDS data was evaluated using Student's *t*-test. The number of SCEs observed in treated cell cultures was compared with that in the untreated cultures using the Mann–Whitney test.

RESULTS

TEM study of particles

The size distribution of the talc samples is reported in Fig. 1. The characteristics of the talc, anatase, crocidolite and chrysotile particles are reported in Table 1. The mean size of the three talc samples was in the ranking order 5725 = 7841 < 5726. The number

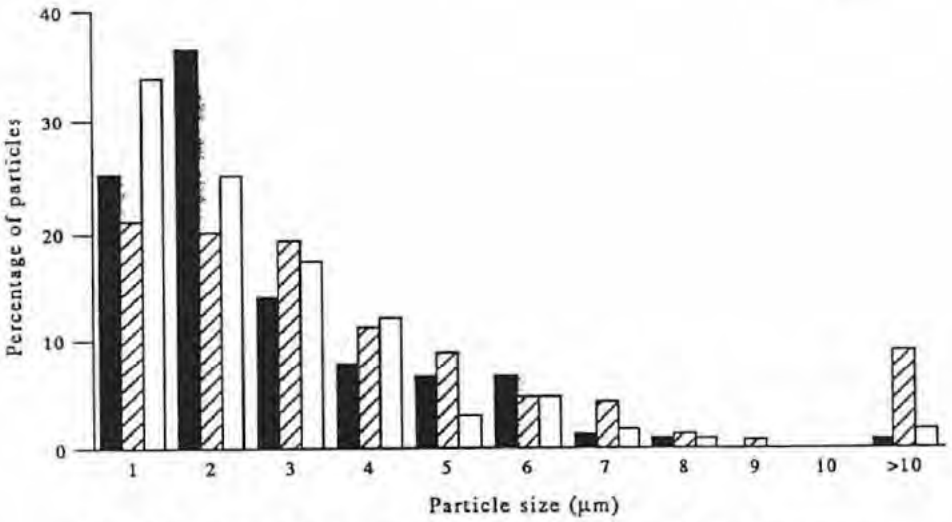

Fig. 1. Size distribution of talc samples no. 5725 (■), no. 5726 (▨) and no. 7841 (□).

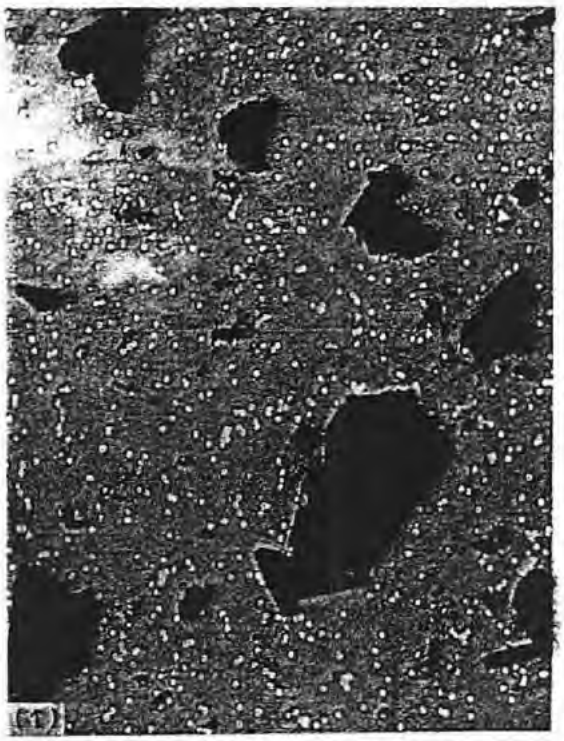

Plate I. Transmision electron microscopy of talc sample no. 5726 (×3000).

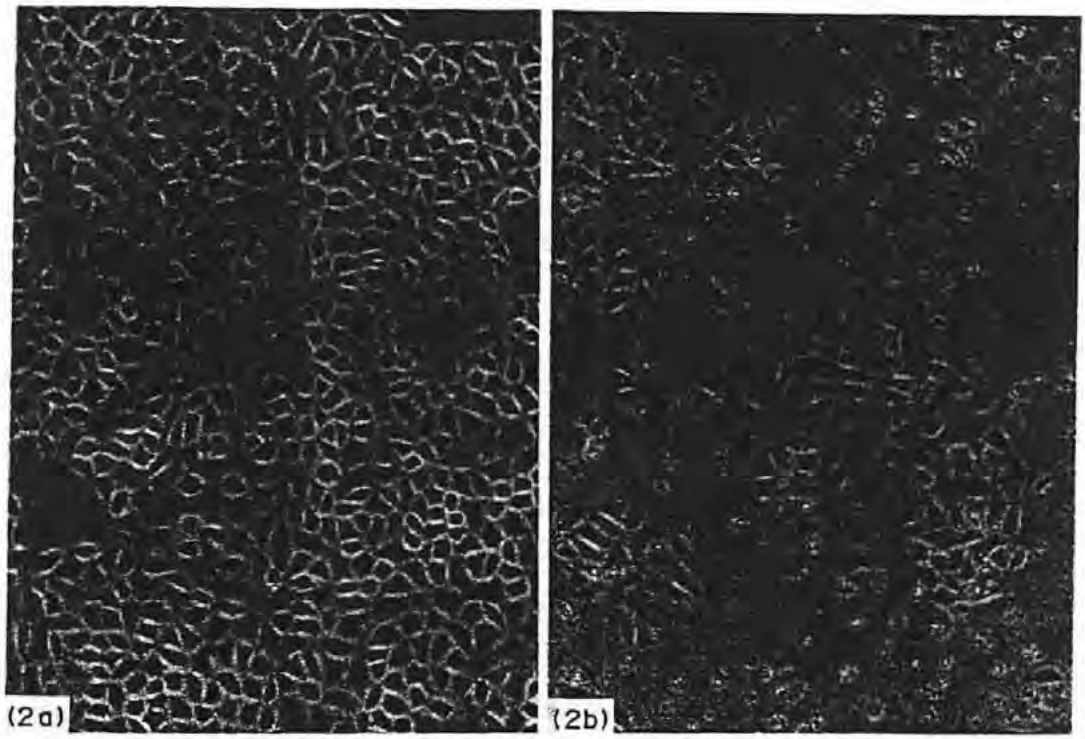

Plate 2. Rat pleural mesothelial cells, (a) untreated or (b) treated with talc particles (arrows) at 50 μg/cm^2 for 48 hr. Phase contrast microscopy ($\times$115).

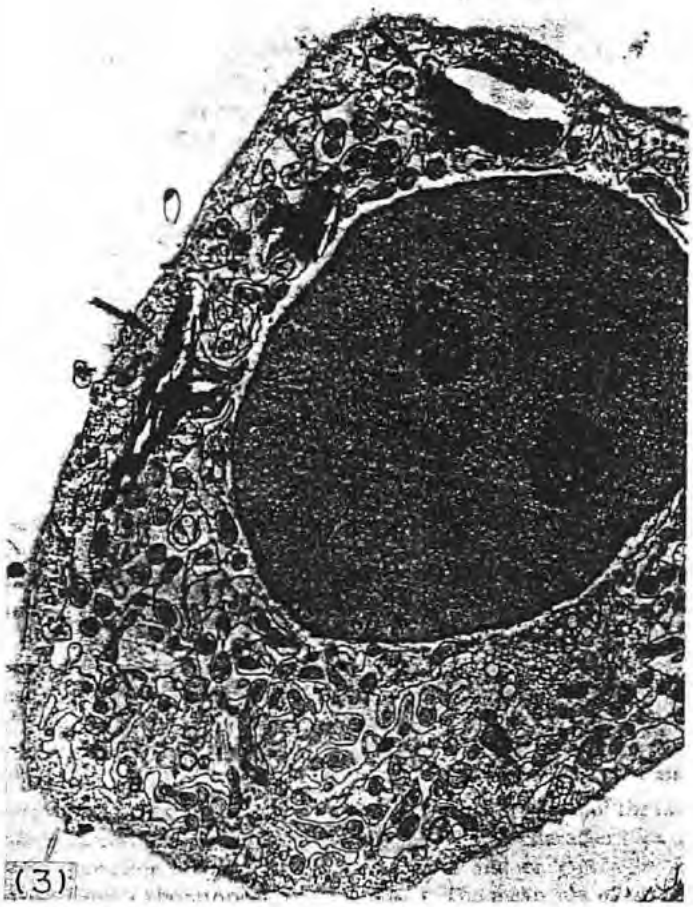

Plate 3. Rat pleural mesothelial cells treated with talc particles (arrows) at 50 μg/cm^2 for 48 hr. Electron microscopy ($\times$6400).

Table 1. Characteristics of the particle samples

Sample	Mean length (μm)	No. of particles/μg	No. of particles of length >4 μm/μg
Talc 5725	2.6	13.0×10^4	2.1×10^4
Talc 5726	4.0	9.8×10^4	2.8×10^4
Talc 7841	2.6	3.3×10^4	0.4×10^4
Anatase	0.7	2.2×10^9	0
Crocidolite UICC	3.1	3.0×10^6	5.1×10^{3}*
Chrysotile UICC	3.2	1.1×10^7	2.8×10^{4}*

*Fibres having a diameter ≤1.5 μm.

of particles per unit weight was in the ranking order 5725 > 5726 > 7841. Therefore, the number of particles having a size greater than 4 μm is approximately the same in two samples and smallest in sample no. 7841. TEM study showed that none of the three samples of talc contained asbestos fibres (Plate 1). The mean length of crocidolite and chrysotile fibres is between those of talc samples 5725 and 7841 and that of sample 5726. The number of crocidolite or chrysotile particles having a length greater than 4 μm is 20–100 times more than that of talc. Anatase is a very small particle having an average size of less than 1 μm with no particle larger than 4 μm.

Structural and ultrastructural studies

No structural change has been observed following treatment of RPMC with talc (Plate 2). It appeared that the number of cells was reduced compared with that of untreated cells but no sign of cytolysis was detected. TEM studies have indicated a capacity of RPMC to ingest talc and anatase particles. Plate 3 shows that talc particles were located in the perinuclear region and organelles did not seem changed in comparison with untreated cells.

Unscheduled DNA synthesis (UDS)

Tables 2 and 3 show the effect of treatment of RPMC with reference particles or talc samples.

Table 3. Unscheduled DNA synthesis in pleural mesothelial cells treated with different talc samples at several doses

Talc sample	Dose (μg/cm²)	Thymidine incorporation (dpm/μg DNA)*† Experiment 1	Experiment 2	Experiment 3
No. 5725	0	1726 ± 189	1299 ± 100	6779 ± 324
	10	1174 ± 285	1310 ± 120	5963 ± 740
	20	1711 ± 72	1289 ± 189	5628 ± 908
	50	1833 ± 144	1232 ± 38	6032 ± 524
No. 5726	0	1652 ± 306	1328 ± 249	6708 ± 357
	10	1681 ± 364	1190 ± 64	6049 ± 666
	20	1419 ± 186	1223 ± 54	6086 ± 534
	50	1527 ± 357	1323 ± 118	5405 ± 420
No. 7841	0	1532 ± 23	974 ± 66	6401 ± 360
	10	1321 ± 40	1053 ± 120	6162 ± 516
	20	1293 ± 12	928 ± 60	6300 ± 241
	50	1271 ± 36	923 ± 98	6450 ± 315

*Experiments 1 and 2 were carried out with a specific activity of *methyl*-^{3}H of 20–30 Ci/mmol; experiment 3 was carried out with a specific activity of 40–60 Ci/mmol.
†Values are means ± SD for six replicates.

Anatase did not enhance UDS in RPMC. Cells treated with crocidolite at 10 μg/cm² or chrysotile at 4 or 10 μg/cm² always showed a significant enhancement of UDS compared with untreated cells. None of the talc samples tested here enhanced UDS.

Sister chromatid exchanges

The numbers of SCEs for reference particles, chemicals and talc samples are shown in Table 4. The control particles, attapulgite and anatase, did not induce a significant modification in the number of SCEs. In contrast, increased numbers of SCEs were observed when RPMC were treated with the genotoxic chemicals mitomycin C and K_2CrO_4. A statistically significant enhancement of SCEs was obtained in cells treated with 2 ng mitomycin C/ml ($P < 0.005$) or 0.5 μg K_2CrO_4/ml ($P < 0.005$). The mean number of SCEs was significantly increased by chrysotile at 1 μg/cm² ($P < 0.005$) or crocidolite at 2 μg/m² ($P < 0.05$), with significant increases occurring in two out of four and three out of eight experiments with chrysotile and crocidolite,

Table 2. Unscheduled DNA synthesis in pleural mesothelial cells treated with different reference particles at several doses

Particle	Dose (μg/cm²)	Thymidine incorporation (dpm/μg DNA)† Experiment 1	Experiment 2	Experiment 3
Crocidolite‡	0	1299 ± 100	1327 ± 57	6086 ± 299
	4	1625 ± 191**	1425 ± 926	9572 ± 463**
	10	1668 ± 53***	1489 ± 203*	8323 ± 308***
Chrysotile‡	0	1495 ± 106	1362 ± 117	5632 ± 326
	4	1744 ± 188***	1498 ± 116*	7590 ± 649***
	10	1646 ± 124**	1598 ± 64***	8157 ± 341***
Anatase§	0	1316 ± 153	6169 ± 760	6579 ± 413
	2	1271 ± 61	6096 ± 705	6785 ± 650
	4	1380 ± 276	6535 ± 565	7214 ± 301
	10	1318 ± 264	6405 ± 480	7764 ± 456**

†Values are means ± SD of six replicates and those marked with asterisks differ significantly (Student's *t*-test) from the corresponding value for untreated cells (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).
‡Experiments 1 and 2 were carried out with a specific activity of *methyl*-^{3}H of 20–30 Ci/mmol; experiment 3 was carried out with a specific activity of 40–60 Ci/mmol.
§Experiment 1 was carried out with a specific activity of *methyl*-^{3}H of 20–30 Ci/mmol; experiments 2 and 3 were carried out with a specific activity of 40–60 Ci/mmol.

Table 4. SCE induction in RPMC treated with reference particles, chemicals and talc samples

Treatment	No. of experiments	Dose (μg/cm^2)†	No. of SCEs/metaphase‡	No. of significant experiments/no. of experiments
Attapulgite	3	0	17.6 ± 2.4	0/3
		20	19.7 ± 1.4	
Anatase	9	0	14.6 ± 2.9	0/4
		2	12.9 ± 3.0	
		5	13.9 ± 2.8	
Chrysotile	4	0	15.2 ± 1.6	2/4
		1	20.2 ± 3.7**	
Crocidolite	8	0	14.9 ± 4.6	3/8
		2	16.8 ± 5.0*	
Mitomycin C	8	0	12.6 ± 1.5	4/4
		2	47.0 ± 12.7**	
K_2CrO_4	8	0	15.4 ± 3.4	4/4
		0.5	38.6 ± 4.2**	
Talc no. 5725	3	0	12.2 ± 1.8	0/3
		2	12.2 ± 1.0	
		5	11.8 ± 2.8	
		10	11.3 ± 0.4	
		15	12.6 ± 2.4	
Talc no. 5726	3	0	12.2 ± 1.8	0/3
		2	12.2 ± 1.8	
		5	9.8 ± 1.0	
		10	12.2 ± 1.8	
		15	12.2 ± 2.3	
Talc no. 7841	3	0	12.1 ± 1.1	0/3
		2	11.9 ± 1.1	
		5	11.0 ± 0.8	
		10	11.9 ± 0.7	
		15	11.1 ± 1.3	

†Except mitomycin C (ng/ml) and K_2CrO_4 (μg/ml).
‡Values are means ± SD for the number of experiments shown, and those marked with asterisks differ significantly (Mann–Whitney test) from the corresponding values for untreated cells (*$P < 0.05$; **$P < 0.005$).

respectively. The number of chromosomes per metaphase and SCE frequencies in RPMC exposed to talc samples 5725, 5726 and 7841 are shown in detail in Tables 5 and 6. No difference in the number of chromosomes per metaphase in treated cells was observed in comparison with untreated cells. Moreover, treatment with several concentrations, from 2 to 15 μg/cm^2, did not increase SCE frequency.

Table 5. Number of chromosomes per metaphase in RPMC treated with three talc samples

Talc sample	Dose (μg/cm^2)	No. of chromosomes/metaphase* Experiment 1	Experiment 2	Experiment 3
No. 5725	0	40.1 ± 2.6	41.0 ± 1.6	41.2 ± 1.5
	2	41.1 ± 1.6	41.2 ± 1.1	40.7 ± 1.5
	5	40.3 ± 1.7	41.1 ± 1.4	41.0 ± 1.5
	10	40.8 ± 1.6	40.8 ± 1.7	40.7 ± 1.6
	15	40.2 ± 1.7	40.9 ± 1.6	41.2 ± 1.8
No. 5726	0	40.4 ± 2.6	41.0 ± 1.6	41.2 ± 1.5
	2	40.3 ± 2.0	41.1 ± 1.3	40.9 ± 1.5
	5	40.7 ± 1.6	40.9 ± 1.4	40.5 ± 1.9
	10	40.7 ± 1.7	40.6 ± 1.6	40.6 ± 1.4
	15	40.5 ± 1.7	ND	41.1 ± 1.7
No. 7841	0	41.1 ± 1.3	41.0 ± 1.6	41.1 ± 1.4
	2	40.7 ± 2.1	41.1 ± 1.2	41.2 ± 1.5
	5	41.2 ± 1.4	41.0 ± 1.7	40.9 ± 1.7
	10	40.7 ± 2.0	40.7 ± 1.8	40.7 ± 2.0
	15	40.6 ± 2.0	40.7 ± 1.8	41.1 ± 1.9

ND = not done
*Mean ± SD of 30 metaphases.

Table 6. Number of SCEs in RPMC treated with three talc samples

Talc sample	Dose (μg/cm^2)	No. of SCEs/metaphase* Experiment 1	Experiment 2	Experiment 3
No. 5725	0	10.1 ± 3.5	13.3 ± 5.7	13.2 ± 5.8
	2	11.4 ± 3.5	11.8 ± 4.1	13.3 ± 4.9
	5	9.0 ± 3.6	11.6 ± 3.9	14.7 ± 6.9
	10	11.4 ± 3.7	10.9 ± 3.5	11.6 ± 5.6
	15	11.6 ± 3.5	10.9 ± 3.2	15.3 ± 5.4
No. 5726	0	10.1 ± 3.5	13.3 ± 5.7	13.2 ± 5.8
	2	11.0 ± 2.9	11.4 ± 4.1	14.3 ± 5.0
	5	9.3 ± 3.0	11.0 ± 3.6	9.2 ± 6.2
	10	10.6 ± 3.4	11.9 ± 3.6	14.1 ± 5.0
	15	10.5 ± 2.8	ND	13.8 ± 5.4
No. 7841	0	12.0 ± 4.3	13.3 ± 5.7	11.1 ± 4.4
	2	10.6 ± 3.0	12.2 ± 3.8	12.9 ± 4.9
	5	10.8 ± 4.9	10.3 ± 3.6	12.0 ± 4.0
	10	12.1 ± 5.4	11.2 ± 4.5	12.5 ± 6.2
	15	11.0 ± 3.8	9.9 ± 3.7	12.5 ± 3.9

ND = not done
*Mean ± SD of 30 metaphases.

DISCUSSION

In the *in vitro* studies reported here we investigated the effects of talc in genotoxic assays. We observed that the three talc samples did not increase UDS or SCEs, or produce aneuploidy in RPMC. In contrast, chrysotile and crocidolite fibres consistently enhanced UDS, as well as increasing SCEs in some of the experiments. This is in agreement with previous observations in our laboratory (Achard *et al.*, 1987; Renier *et al.*, 1990). SCE enhancement was also obtained after treatment of RPMC with mitomycin C and K_2CrO_4, agents previously known to induce SCE (Darroudi and Natarajan, 1989; Kato and Shimada, 1975; Levis and Bianchi, 1982; Littlefield *et al.*, 1979; Perry, 1980). The negative reference particle, anatase, did not increase either UDS or the frequency of SCEs in comparison with untreated RPMC.

In spite of the fact that talc is a magnesium silicate, as are chrysotile fibres, the *in vitro* responses of the two particles are different. As far as the mechanisms of genotoxicity of particles are concerned, several factors might account for the different responses, in particular phagocytosis, granulometry and the shape of the particles. Several questions can be addressed.

First, is the lack of genotoxic action of talc due to the absence of phagocytosis? Phagocytosis seems to play an important role in the genotoxic effect of particles, because fibres phagocytosed could interact with the mitotic spindle (Hesterberg and Barrett, 1985) or chromosomes (Wang *et al.*, 1987). This may then induce aneuploidy by chromosomal missegregation (Hesterberg and Barrett, 1985; Palekar *et al.*, 1987). Our TEM study showed that RPMC can ingest talc particles. This cellular process has been also observed with chrysotile and crocidolite asbestos fibres (Jaurand *et al.*, 1979 and 1983). Despite phagocytosis, talc did not induce aneuploidy since the number of chromosomes per metaphase in talc-treated cells was not different from that in untreated cells (Table 5). Therefore, the lack of chromosomal

damage might be related to different mechanical or physicochemical properties of talc in comparison with mineral fibres.

Secondly, is the absence of genotoxic action due to the size of the talc particles? From the data reported in the literature, the carcinogenic potency of particulate matter seems to be dependent on both shape and dimension. For example, Stanton *et al.* (1981) have reported that after intrapleural inoculation into the rat, the frequency of pleural sarcomas was dependent on the number of fibres less than 0.25 μm in diameter and more than 8 μm in length. Moreover, an *in vitro* assay has shown that thick glass fibres were more efficient than thin fibres, on a per number basis, in transforming Syrian hamster embryo cells. In addition, no transformation was obtained when the fibre length was reduced to 0.95 μm (Hesterberg and Barrett, 1984). In contrast to asbestos fibres, talc does not have a fibrous shape, but rather a polygonal form. Fibre samples containing long fibres can be deposited in the airways because of their small diameter, whereas respirable talc particles with a diameter higher than 5 μm do not reach the deep lung. The absence of an *in vivo* effect of talc might also be due to the small size of the particles. The size and number of particles per unit weight are different in the three talc samples. Granulometric study of the talc samples showed that the mean size was in the ranking order 5725 = 7841 < 5726 and of the same order as that of asbestos fibres. However, the number of long (>4 μm) particles is much higher in asbestos samples than in the talc samples used here.

The three talc samples did not enhance UDS or induce SCEs in comparison with untreated RPMC. This is in contrast to the results with asbestos, especially with regard to the UDS assay in which a significant response was observed with both types of asbestos fibres. The SCE results seem less convincing; in effect, no consistent positive enhancement of SCEs was found with crocidolite, thus lessening the significance of the negative response obtained with talc. However, our observations are in agreement with *in vivo* data reported by Stanton *et al.* (1981) and with our previous results obtained with sample no. 7841, which showed that talc did not produce tumours following intrapleural inoculation (Endo-Capron *et al.*, 1990), as well as with *in vitro* results that showed that talc did not induce chromosomal effects in mammalian cells *in vivo* and *in vitro* (IARC Working Group, 1987).

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INTERNATIONAL SOCIETY OF
REGULATORY TOXICOLOGY AND PHARMACOLOGY

February 12, 1993

John E. Bailey, Ph.D.
Acting Director, Office of
Cosmetics and Colors
Department of Health & Human Services
Public Health Service
Food & Drug Administration
Washington, DC 20204

Dear Dr. Bailey:

Following your letter and our telephone conversation regarding a co-sponsorship of this Society and FDA of a symposium on talc, I enclose a brochure describing the Society and its goals. Our Council has agreed to pursue the concept and our President Dr. Gio Gori will call you in this regard.

Topics of this character are within the scope of ISRTP and we are interested in any measure that encourages the use of sound scientific information in regulatory decisions. Our official Journal *Regulatory Toxicology and Pharmacology* provides a medium for publication of any reports of meetings we co-sponsor.

I trust we may be of assistance to your Agency in this respect.

Sincerely,

C. Jelleff Carr

C. Jelleff Carr, Ph.D.
Secretary

CJC/sw

Enclosure

cc: Dr. Gio Gori

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OF (Organization)

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Discuss ideas

Kind of issue – They like –

Dr Gori –

Mtg w/ Com
4/15/93 –

Follow-Up Action Required? No _____ Yes _____

Completed _____

C:\JB\PERS\PHONE-2.FRM

NOTE OF TELEP

Date 2/11/93

Name _____

Phone Number _____

Address:

_____

_____

_____

_____

MEMORANDUM OF CALL

Previous editions usable

TO: John

☒ YOU WERE CALLED BY– ☐ YOU WERE VISITED BY–

Dr. Gori

OF (Organization)

☐ PLEASE PHONE ▶ (b) (6) [redacted] ☐ FTS ☐ AUTOVON

☐ WILL CALL AGAIN ☐ IS WAITING TO SEE YOU

☐ RETURNED YOUR CALL ☐ WISHES AN APPOINTMENT

MESSAGE

1: 11. . Ottis, about

Nature of Conversation

Call from Dr. Carr – Discuss details –
6 mos – do sooner –
Speakers – reading knowledge
Booklet – Useful
Journal – Special booklet – general
FDA – Contribution – Nominal contribution
Audition – Where – Auditorium –
Try – NIH i.e. DCES depends –
# of people – Interest – broad
Industry contribute $ – Prob OK –
Get OK from bosses – Should announce
from

Follow-Up Action Required? No _____ Yes _____

Completed _____

C:\JB\PERS\PHONE-2.FRM

$20K from ISSGO

$10 K from FDA

Total cost ≈ 50-70 K

Cost to attendees - Keep low ~ $100

or Kids can't attend

10 K 100 x 100

100-120 - Scale fee - Govt vs Ind. rates

$20-25 K from industry -

3-4 months - Fast track -

MCS - May not have attendance because of lawyers -

Selection of speakers -

Appeal names to list of topics -

Tentative basis so far -

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Washington DC 20204

February 1, 1993

Dr. C. Jelleff Carr
(b) (6) [redacted]

Dear Dr. Carr:

This letter is in follow-up to your conversation with Dr. Linda Tollefson concerning the Food and Drug Administration's interest in co-sponsoring a scientific symposium with the International Society of Regulatory Toxicology and Pharmacology on talc. Talc is used as an ingredient in many food, drug and cosmetic products as well as certain medical devices and, as such, it comes under the regulatory purview of the FDA. It also is used in many industrial applications where worker exposure is a consideration.

While talc is considered a safe ingredient for most applications, there is some concern about potential health risks to humans under certain conditions of use. For example, a recent study conducted by the National Toxicology program found that inhalation of talc caused cancer in the test animals. In a recent epidemiology study, the researchers reported an association between perineal exposure to talc and ovarian cancer.

Because of the wide use of talc and the broad interest in the safety of the ingredient, we feel that there will be sufficient interest to support a symposium. The following is a suggested format and topics for a 1-1/2 day symposium as envisioned by our task group:

Symposium Title: Talc: Production, Uses and Health Perspectives.

Day 1:

1. Keynote speaker to introduce the topic and present the reasons for holding the symposium. Provide some background about studies conducted on the safety of talc (historical perspective). Speaker also likely to serve as moderator.

2. Production of talc - How and where it is obtained (mined), processed for use in different products and quality control including steps to control and monitor asbestos contamination.

3. Uses and regulatory status of talc (possibly presented in two parts).

   a. Discussion of different types of products and the types of talc used.

   b. Presentation on the regulatory status of talc as used in foods, drugs, cosmetics and medical devices.

4. Health Perspectives - Recent NTP inhalation study to be presented by someone from NTP involved in the study.

5. Health Perspectives - Critique of NTP inhalation study considering issues raised and relevance to human exposure.

6. Panel discussion Q and A.

Day 2:

1. Historical overview of epidemiology studies (possibly in 2 parts)

   a. Epidemiology studies of occupational exposures (inhalation).

   b. Epidemiology studies on ovarian cancer.

2. Recent studies conducted by Dr. Harlow (1989 and 1992) - Invite Dr. Harlow to speak.

3. Discussion of the pros and cons of meta-analysis as a statistical tool in measuring correlations in epidemiology studies.

4. Panel discussion Q and A.

5. Moderator wrap-up and close.

Should ISRTP decide that a symposium on talc is of interest, we can discuss the details in greater depth. Please feel free to call me (202-205-4530) or Dr. Tollefson (202-205-5652) if you have any questions.

Sincerely,

John E. Bailey, Ph.D.
Acting Director, Office of
Cosmetics and Colors

cc:
HF-50 (McCarthy
HFD-812 (McCannon)
HFS-2 (Archer)
HFS-16 (Lorentzen)
HFS-22 (Elliot)
HFS-101 (Milstein)
HFS-125 (Dennis)
HFS-728 (Tollefson/Altekruse)

RD:JEBailey:HFS-100:1/26/93
Finalized:jdc:2/1/93

1/25/03 Linda Tollefson

ISRTP (b) (5) [redacted]

Next Feb. 9th – Stating purpose
meeting

(b) (5) [redacted]

(b) (5) [redacted]

Secretary of ISI

(b) (6) C. Jelleff Carr Ph.D [redacted]

(b) (5) [redacted] 1054

Request Co-sponsor Sci. Symposium –

1/25/93

Contract CDER Prescription & CDRH Ann Torrese

ISRTP - Needs a definite yes -
Local Time -
Do administration part -
Charge Fee
Honoraria if money left over -
Suggest not give

1 1/2 days

In Virginia Hotel
Registration
Split registration — Govt — Clinical Trial

$250 - Too high (PDLI would not →

Need estimate - L.T. will call back

$100 - $150 OK
Industry costs -

CPSC?? Diapers -
Tampons - CDRH?

NIOSH - OSHA - CPSC - NCI - NCTR - NIEH
CTFA -

SCC - Symposium - Talc -

FDA - 20 - 30
other - 10 - 15
Mark at 30-50

Financial Support - Dept./OC

Corporate Sponsors?

Title of Symposium —

Ron society?
Ron Gades MD

Talk: ~~Current~~ Symposium ~~Conceptual~~ Production, Use ~~Manuf, Applications~~
and Health Perspectives —

(0) Keynote Speaker - Why are we here — Health Perspective

Topics: (1) Production — What/when/How —
→ CTFA — Suggest
Cover Asbestos — Particle Size —
Applications

(2) [Regulatory Overview —
Uses including GI]

1st Day

(3) Health Perspective —
NTP → Inhalation Study — Animal
Literature Search —

(4) Health Perspective —
Critique NTP Study —
Issues presented by study —
Relevance to use
Point/Counterpoint —
EPA? NIOSH? Occupational Exp.
and relevance

Panel

(5) Epi Studies —
Sr Occupational-Field Overview of Studies to 1989
JL NIOSH Epi - Ovarian

2nd Day (6) Harlow — 1989 & 1992 —

Clinical Oncologist

General Overview (7) Meta Analysis — Somebody from Hopkins

Bernstein
✓ John Baylar (Janet Springer)

⑧ Panel Discussions

⑨ Wrap-Up — Who? Moderator Keynote Speaker

Lou Lowitzer

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

: 2

Ms. Janet Springer
Director, Division of Mathematics
Food and Drug Administration
FB8, Room 2017A
200 C Street, S.W.
Washington, D.C. 20204

Dear Ms. Springer:

I find this quite unconvincing, Yes, it attains statistical significance (barely), but that is not enough for a hypothesis that has little solid biologic rationale. (Little in this context.) Also, the various subgroups - direct application; daily; more than 10 years - are highly dependent in a statistical sense; they do not add much in the way of independent evidence. The 14% of women at highest risk (OR 2.8, CI 1.4-5.4) is a little more eye - catching, but not much.

Some specific weakness - "Ovarian cancer" is a huge grab - bag of tumor types of almost certainly different causes, even when one limits the scope to epithelial tumors. Further, not all were malignant, but there is little analysis of either type or malignancy. The similarity of ORs in Table 5 is for me a heavy blow to any cause - effect interpretation. I just do not expect the same biologic effect of a single agent on each in a list of distinct outcomes.

There appear to be only 33 cases in the "high risk" group, vs. perhaps 12 in the corresponding control group, so that small biases may be important. For example, there is no comment on what the interviewers and/or subjects may have known about the null hypothesis and alternatives.

The OR is a useful statistical tool here because of its nice mathematical properties, but it carries a misleading sense of the absolute magnitude of risk, especially when base population exposures are high. We may take the risk ratio as essentially the same as the OR, or possibly in the range 1.0 - 2.1, but the absolute risk (if any) is small.

The one really striking OR in Table 1 does not make biological sense; I can think of no plausible reason why the risk should be far higher for women with one child than for those on either side of one. Of course, numbers are small for this.

I am a little puzzled that the crude OR (Table 1) and adjusted OR (Table 2) were identical, and with identical CIs. Perhaps there has been a serious numeric error, or the chosen covariates were utterly ineffective. (Of course, covariates may have been equally distributed over exposure categories, but that seems unlikely.) I do not know enough about ovarian cancer to tell whether there are reasonable covariates for this purpose, and this matter should be examined pronto.

The modeling for adjustment is critically dependent on underlying assumptions about linearity (logistic scale) and independence. There is no statement that these were checked. This might be important, specifically, in Table 3 and in the adjustments for age (where linear effects would surprise me).

What I see in Table 3 is that from the top to the bottom panel, ten cases and nineteen controls were redistributed from "greater than 10,000" to lower exposures. (There may have been other changes, but this is the biggee). In other words, the whole effect (not just here, because of dependencies) may depend on a difference of ten subjects with very high exposure.

The critical (combined) OR in Table 6 may have two problems. First, I could not reproduce the 1.3 by hand calculations, though I may have made numeric mistakes. Second, what we need to judge the present work is the OR for all other studies, excluding the present one.

The Discussion drivels on far too long.

In the end I think, "Well, maybe." The evidence is not strong enough to take any public health action, but it is sufficient to worry a little, and perhaps to support larger, better designed studies.

Sincerely,

John C. Bailar III, M.D., Ph.D.

Lorentzen

Date October 1, 1992

From Bob Blodgett
Biometric and Risk Assessment Branch, HFF-118
Division of Mathematics

Subject Meta-analysis for Ovarian Cancer in Harlow et al

To Janet Springer
Division of Mathematics, HFF-110

Harlow et al report the results of a case-control study. They calculate the odds ratios for several subsets of their data and discuss problems inherent in a study of this nature.

This discussion is limited to the small portion on meta-analysis. No attempt is made to evaluate any of the six studies. If any of the individual studies are suspect, the results of the meta-analysis also becomes suspect. Also, it is unclear whether the stated differences have a real effect. With many more studies a heuristic attempt to evaluate the effect of these differences might be possible. Table 6 of Harlow et al has a few minor misprints. After some notation a corrected version is given below.

	Talc	No Talc
Case	n_{11}	n_{12}
Control	n_{21}	n_{22}

Studies	n_{11}	n_{12}	n_{21}	n_{22}	Odds Ratio	Asy 95% CI
Cramer et al	92	123	61	154	1.9	1.3, 2.8
Hartge et al	67	62	100	61	0.7	0.4, 1.1
Whittemore et al	97	91	247	292	1.3	0.9, 1.8
Harlow and Weiss	49	67	64	94	1.1	0.7, 1.7
Booth et al	141	76	256	178	1.3	0.9, 1.8
Harlow et al	114	121	94	145	1.5	1.0, 2.1
Overall	--	--	--	--	1.3	1.1, 1.5

Hartge et al was changed to use their "No talc mentioned" and "Any talc mentioned" lines rather than subtracting "Any talc mentioned" from the total. Whittemore et al was changed to conform to their table 6. Also, their odds ratio was not adjusted for parity to be more comparable with the other studies. The odds ratios and asymptotic confidence intervals were recalculated for all studies.

For clinical trials, where the location is unimportant, the methods are kept identical and the same analysis is used on all the data, there is little problem with combining the data. Consequently, any errors will not be expected in the calculations, but in their applicability. The basic question is the following. Are the studies similar enough to justify combining? Surveys require extensive effort to get consistent, reliable results which allow comparisons of survey sites. The basic premise of meta-analysis is that all these precautions are an unnecessary waste of time. Either survey sampling or meta-analysis is badly mistaken.

Rather than presenting allegorical and theoretical evidence to support the caution of survey sampling the differences in the studies in table 6 are explored. First, these six studies were centered in London, Washington, Boston, Seattle and San Francisco. These cities were not the product of a random selection. Thus, if location matters, it is unclear what population a combination of these six represents. There are several reasons for suspecting location may matter. The racial and economic status of the people may differ among locations. Racial differences may not be relevant, but the fact that three studies were restricted to white women suggests they can not now be ignored. Race may be a surrogate for economic status which could effect the amount, type, and pattern of use of talc. Also, the brands of talc, or at least their market shares, may differ among locations and economic groups.

Greenland (1987) suggest a chi square test for homogeneity. With all 6 studies this test gives a chi square of 12.2 with 5 degrees of freedom. This result suggests that the studies are not homogeneous. Also, the ratios of talc use among the control groups are quite varied. The following review of some apparent differences may be helpful, but does not imply the stated differences are the important ones.

Hartge et al conducted their study in Washington, D.C. and "talc exposure was not a major focus of this study..." One difference from the other studies is that talc users in this study could have used talc anywhere. The five other studies asked about perineal talc use. Another difference seems to be race. The letter reporting this study did not mention any selection based on race. If the race in the study reflected the composition of Washington, D.C. at that time, it would be about 70% black. Cramer et al, Harlow and Weiss, and Harlow et al were all restricted to white women. Whittemore et al had at most 6% black and orientals according to their table 1. Booth et al was in England. Consequently, this study seems too different from the others to include.

Booth et al conducted their study in London and Oxford, England; the other five were in the United States. With possibly

different regulations and different mining locations talc in England may be a different substance from talc in the United States. Certainly the racial mix, economic status and culture of the populations are different. Thus, this study seems too different from the others to include.

Whittemore et al had a little over half their controls as women who were hospitalized. The other three remaining studies used controls only from the general public. The controls for the stated odds ratios included both groups.

The Harlow and Weiss study was restricted to borderline ovarian tumors. Whittemore et al excluded women with borderline tumors. Cramer et al and Harlow et al included woman with borderline tumors as well as others. Cramer et al had 39 of 215 with borderline tumors. According to table 5 Harlow et al had 62 of 235 with borderline tumors. I do not know if this should prohibit combining these studies.

The Cramer et al and Harlow et al were performed in the same city and some of the authors were the same. Although the number of participating hospitals decreased from 12 to 10, the most evident difference is the time of the studies. Since "... ovarian cancer was greater in women using talc products before 1960 ...," what these two studies may be indicating is that the situation is improving after the change in 1960. The difference in the logs of their odds ratios is not significant.

In general, several studies all showing a result is significant may be more satisfying than just one. It seems less likely several groups of investigators would all error. Meta-analysis lacks this justification. It combines several studies without significant results and concludes that if they were all done together they would have produced a significant result.

Studies	n_{11}	n_{12}	n_{21}	n_{22}	Proportion of control	95% CI
Cramer et al	92	123	61	154	.28	.22, .34
Hartge et al	67	62	100	61	.62	.55, .70
Whittemore et al	97	91	247	292	.46	.42, .50
Harlow and Weiss	49	67	64	94	.41	.33, .48
Booth et al	141	76	256	178	.59	.54, .64
Harlow et al	114	121	94	145	.39	.33, .46

Why should the above table be included? The odds ratio adjusts for any difference in proportions. Yes, but what we are searching for is differences in the populations or in the studies. If everything were the same, the proportions would be fairly close. The two studies that seemed most deviate have confidence intervals that don't over lap the others.

ROUTING AND TRANSMITTAL SLIP Date 5 Sept 2, 1992

TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
1. Louis Pribyl		
2. HFF156		
3.		
4.		
5.		

✓ Action	File	Note and Return
Approval	For Clearance	✓ Per Conversation
✓ As Requested	For Correction	✓ Prepare Reply
Circulate	For Your Information	See Me
Comment	Investigate	Signature
Coordination	Justify	

REMARKS

Dr. Bolger suggested that I forward this letter to you. I would appreciate a copy of your reply.

Hank Davis
HFD-8

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post) | Room No.—Bldg. | Phone No.

5041-102 * U.S. GPO: 1988 — 262-080

OPTIONAL FORM 41 (Rev. 7-76) Prescribed by GSA FPMR (41 CFR) 101-11.206

Dear Sir,(Madam)

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Thank you (b) (6)

enc. 2

RECEIVED
OSTP EXECUTIVE
SECRETARIAT STAFF
92 AUG 32 PM 5:13

245-003-C2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

April 30, 1993

(b) (6)

Dear (b) (6):

This is in reference to your letter of October 27, 1992, in which you expressed your concerns about the safety of the substance **TALC**, as this ingredient is employed in over-the-counter medications.

We regret the passing of your husband and understand that the circumstances surrounding his death have quite naturally increased your interest in the subject of talc and the health consequences associated with its use. The Food and Drug Administration (FDA) shares your concerns about the safety of cosmetic and drug products formulated with talc that are marketed in the United States.

Over-the-Counter (OTC) medications...whether oral or topical...are regulated by the Office of OTC Drug Evaluation within FDA's Center for Drug Evaluation and Research (CDER) rather than by the Office of Cosmetics and Colors, which operates within FDA's Center for Food Safety and Applied Nutrition (CFSAN). Therefore, I am unable to answer your question with the specificity that you might prefer. I will, however, attempt to provide you with some general information about talc and some perspectives concerning its use in cosmetic products.

The Food, Drug, and Cosmetic Act (FDCA) of 1938 defines "cosmetics" as articles intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance without, however, affecting the structure or any function of the body. Products that are cosmetics but are also intended to treat or prevent disease, or affect the structure or functions of the human body are considered "drugs" and must comply with both the drug and cosmetic provisions of the law. Most currently marketed cosmetics which are also drugs are "over-the-counter" or OTC drug-cosmetics; several, however, are "new drugs", for which safety and efficacy had to be proven to FDA by means of a "new drug application" or NDA before they could be legally marketed.

The regulatory authority provided to FDA by the FDCA with respect to cosmetics is limited when compared to the regulatory authority for drugs. The FDCA does not require mandatory premarket safety testing of cosmetic products or the raw materials used to manufacture them, nor does it require manufacturers to register their establishments and products or to file reports of adverse reactions with FDA. While the cosmetic industry is largely self-regulated, the FDA does have the authority to take legal action against a cosmetic product or ingredient under the adulteration (Section 601) and misbranding (Section 602) provisions of the FDCA. The FDA can, and does take regulatory action whenever a risk to consumers is established by scientific and/or medical determination, and the evidence can be supported in a court of law.

While the FDCA does not require premarket approval for cosmetic products, we believe that most cosmetic firms do, in fact, conduct safety testing before marketing new products. Products, whose safety is not adequately substantiated before marketing, are required by regulation to include on the label the following statement: "Warning - The safety of this product has not been determined".

Talc has historically been used in both drug and cosmetic applications. Its incorporation as a pharmaceutical excipient in over-the-counter preparations has not been restricted to oral dosage forms intended for human ingestion but also includes various semisolid formulations, such as diaper-rash ointments, intended for topical application. Talc has also been employed to dust surgeons gloves, although this practice may have fallen into disfavor, as you allude to in your letter. Talcum Powder, the primary use for talc in cosmetic applications, is one of the most widely used toiletries, especially in after-bath preparations, because of its absorbent, mildly water-repellant, anti-chafing properties as well as the improvement in skinfeel (i.e., "slip") imparted to the skin upon talcum powder application. Compositionally, talcum powder is usually formulated with talc, fragrance, other emollient substances, and, possibly, antibacterial agents.

Talc, the predominant component of talcum powder, is a compositional variant of the complex mineral compound "magnesium silicate", which is mined in Italy and France, as well as in the United States. In the early 1970's, the specifications for cosmetic-grade talc were largely rewritten by the Cosmetic Industry to mandate a so-called "platy" talc content (i.e., talc having flat vs. fibrous particles) of at least 90% and a talc free of other detectable fibrous minerals, including asbestos (c.f., copy of CTFA Cosmetic-Grade Talc Specification, accompanying this letter).

Overall, it is generally believed that the use of talc for external cosmetic applications, employed in a well-ventilated area and according to the manufacturer's intended use instructions, is safe. However, the medical literature does contain reports that argue in favor of prudence and moderation in the use of talc. Some medical authorities have recommended that the use of talcum powder on infants should be discouraged, due to the possibility of accidental, massive acute inhalation of powder and subsequent suffocation. There have also been some associations reported in the medical literature between frequent direct female perineal talc dusting over a protracted period of years and an incremental increase in the statistical odds of subsequent development of certain ovarian cancers. Occasionally, there have been occupational reports of chronic inhalation of talc dusts (i.e., a product abuse) leading to pulmonary fibrosis. However, the type of medical history which followed the surgery undergone by your husband in Germany more than 30 years ago, as you described it to us, is fairly unusual.

I trust that the information contained in this response will prove helpful to you. If you have specific questions about the safety profile of talc in orally-ingested drug products or topical over-the-counter (OTC) drug products, you may address them to Dr. William B. Gilbertson, Director, Division of OTC Drug Evaluation, Office of OTC Drug Evaluation (HFD-210), The Center for Drug Evaluation and Research (CDER), U.S. Food & Drug Administration, 7520 Standish Place, Rockville, MD 20855.

Sincerely yours,

Stanley R. Milstein

Stanley R. Milstein, Ph.D.
Special Assistant to the Director
Office of Cosmetics and Colors
U.S. FOOD & DRUG ADMINISTRATION

Enclosure

cc:
HFS-100 (Bailey) ✓
HFS-105 (Halper)
HFS-128 (Bronaugh)
HFS-128 (Kornhauser)
HFS-226 (Pribyl)
HFD-365 (Davis)
HFD-210 (Gilbertson)

SRMilstein:ccv:4/30/93

(b) (6) [redacted]

HD
Talc

Dear Sir,(Madam)

I am concerned about the use of talc. in over the counter medications.

My late husband died from the ravages of talc to his digestive system over eleven years ago.

I was horrified to learn that this deadly 'foreign body' is still being used in medication simply because it is useful in mixing the ingredients to a satisfactory consistency.

I wrote to one of these companies that had talc. in their medication without letting them know of my concerns. They wrote back that talc. was safe because the FDA checked for abestos, besides, talc was not inhaled into the lungs so it had to be safe for ingestion.

I want to point out that their was no cure for my late husband. The talc. glued the viscera together so there was no way the doctor's could save him.

Enclosed you will find self explanotory findings in a copy of my husband's operation.

I would like to be assured by your organization that talc. in over the counter medications is 100% safe.

Thank you (b) (6) [redacted]

enc. 2

RECEIVED
OCRS EXECUTIVE
SECRETARIAT STAFF
92 AUG 32 PM 5:13

245-003-C2

NAPLES COMMUNITY HOSPITAL, INC.

REPORT OF OPERATION

215-2

LAST NAME	FIRST NAME	MIDDLE NAME	AGE	DATE	HOSP. NO.
(b) (6) [redacted]					(b) (6) [redacted]

SURGEON	ASSISTANT	ANESTHESIOLOGIST	TECHNICIANS
W. BAILEY, M.D.	T. HAVIG, M.D.	J. CAMPOAMOR, M.D.	

Preoperative Diagnosis: High jejunal obstruction due to postoperative adhesions, reaction to foreign body granuloma - talc.

Postoperative Diagnosis: Same, plus frozen abdomen in multiple areas of obstructio

Operation: Exploratory laparotomy, closure of one transverse colon enterostomy, #16 angiocath jejunal hyperalimentation catheter.

Gross Findings and Description of Procedure:

This patient was given general endotracheal anestheia, a Foley catheter was inserted into the bladder, the whole abdomen was scrubbed and draped with special care to cover the colostomy in the right upper quadrant and isolate it from the main incision including Steri-Drapes. Incision made through the old laparotomy scar, left paramedian, through the skin and fat which was minimal down to the fibrous muscle wall and this was carefully incised the full length looking for an opening in the peritoneal cavity. This was finally accomplished with a small rent in the transverse colon distal to the colostomy which had proved to be no problem and this was closed with #3-0 catgut reinforced with silk. It was practically impossible to place the hand inside the abdomen because of the rigid loops of the small bowel that were fixed to the parietal peritoneum and also adjacent loops with marked edematous reaction. The attempt was made to expose the prior gastroenterostomy that resulted 30-40 years ago, a subtotal gastric resectio with Billroth II, but it was impossible to separate any of the organs, one from the other. The pathologist was standing by for any possible frozen section, was asked to grossly inspect the internal abdomen. He had gowned sterilely so he could approach the operating table more closely and it was demonstrated to him this tremendous adherence and complete amalgamation of all the viscera one to the other and it it impossible to separate by either blunt or sharp dissection. Prior to this procedure, on the initial laparotomy, a diagnosis of talc granuloma was made grossly at the operating table to account for the original obstruction and the complete gluing of the viscera together and this was proven by microscopic examination showing bifringent crystals proved to be magnesium silicate used as a talcum powder inside the gloves at surgery years and years ago. He and the assistant surgeon, Dr. Havig, agreed that no definitive surgical procedure could be accomplished. The most proximal loop of bowel was selected and #16 angiocath was inserted distally into the lumen of the bowel, sutured in place with #3-0 silk and brought out the left abdomen for possible hyperalimentation. Even this may prove futile if the bowel is completely obstructed in many areas below. The sponge count correct. Wound was closed in one layer using #2 dexon through and through stitch reinforced

NCH 124 REV. 7/76

Signature of Surgeon

INFORMATION ON TALC

Talc and asbestos are different forms of the naturally-occurring mineral, magnesium silicate. They are often found intermingled in nature.

The talc which is used in products regulated by the Food and Drug Administration (FDA) is safe; we have no evidence of hazard.

Talc has historically been used as a coating for polished rice. Other uses include paper and paper products, cotton fabrics used in dry food packaging, as a chewing gum base, and as an anti-sticking agent for molded foods. Talc is also used in cosmetic products, such as talcum powder.

In 1973, the FDA proposed that talc which is used in foods be free of asbestos particles. At that time, there was no demonstrable evidence that ingested talc which contained asbestos particles was hazardous. However, the future regulatory status of talc which is used as a coating for rice was in question. Subsequent to the publication of this proposal a method was devised for separating asbestos from talc.

In 1977, a sampling of foods which contained talc demonstrated that asbestos contamination was rare and, when found, was in very small amounts (less than .1%). Although there has been no direct study of the effects of ingested talc, it is not considered to be problematical.

In 1982, a study of talc conducted by the Federation of the Society for Experimental Biology (FASEB) revealed that pure talc is not carcinogenic in man or animal.

****

John-

Attached is some of the documentation that (b) (6) had provided re. her husband's surgery (+ the "talc connection") along with her earlier letter. Our response was to a second letter received on October 27, 1992.

SRM
5-3-93

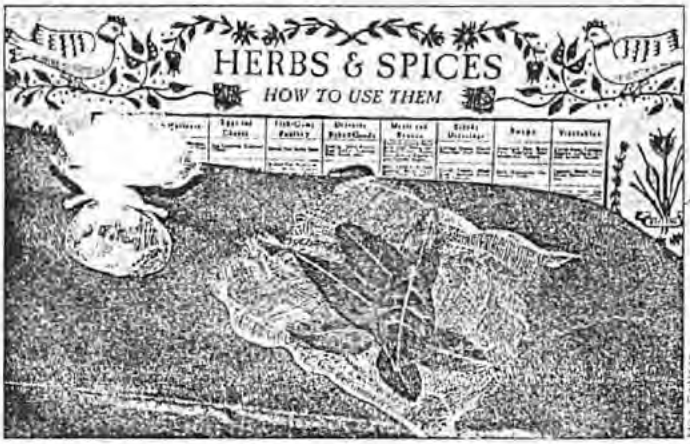
valves should not undergo MRI, but other kinds of heart valves are safe. Problems can arise if one has a clamp for a brain aneurysm, a surgically implanted neurostimulator (with wires inside the body), certain ear implants, or shrapnel near a great vessel, a nerve, or anywhere in the head.

Metal items that are usually problem-free include tooth fillings, clips used in surgery to stop bleeding, and joint replacements; however, it is important to emphasize the need for each case to be considered individually.

Take the Bay Leaves Out

Dear Dr. SerVaas:

I have noticed that many recipes call for bay leaves, but do not advise you to remove them before serving the dish. Can't bay leaves be harmful if swallowed, and if so, shouldn't people be informed that they are supposed to remove them?



I have enjoyed the *Post* for many years, and I am sure that you will want to say something about this, because you have helped so many people in the past.

D. Andrew Lentz
Santa Fe, New Mexico

Thanks for reminding us again about bay leaves. If swallowed, these leaves can be as dangerous as glass. They're not digestible and can have sharp, serrated edges. They never should be left in stews.

Numerous people have gone to the emergency room because they accidentally or intentionally consumed a bay leaf that should have been removed before eating.

One emergency room in Evanston, Illinois, reported five cases of bay leaves lodged in the throats of unsuspecting diners in two years. Another case was reported in which an ingested bay leaf had cut into the muscle of the esophagus. Bay leaves can also cause problems further down in the digestive tract. One person reported to the emergency room with appendicitis-like symptoms caused by a bay leaf and required surgical removal. Another man developed excruciating pain upon defecation because a bay leaf became lodged in his rectum.

Prevention is the key here. Swallowing a bay leaf can be potentially life-threatening, and no risk needs to be taken if simple precautions are followed. If you are preparing a dish that calls for bay leaves, put the bay leaves in a small mesh bag that can be removed when cooking is completed. Watch for bay leaves when you are dining out. Also, if you suspect that you may have swallowed a bay leaf, don't wait to get medical help.

* Is asbestos still in Talcum powder

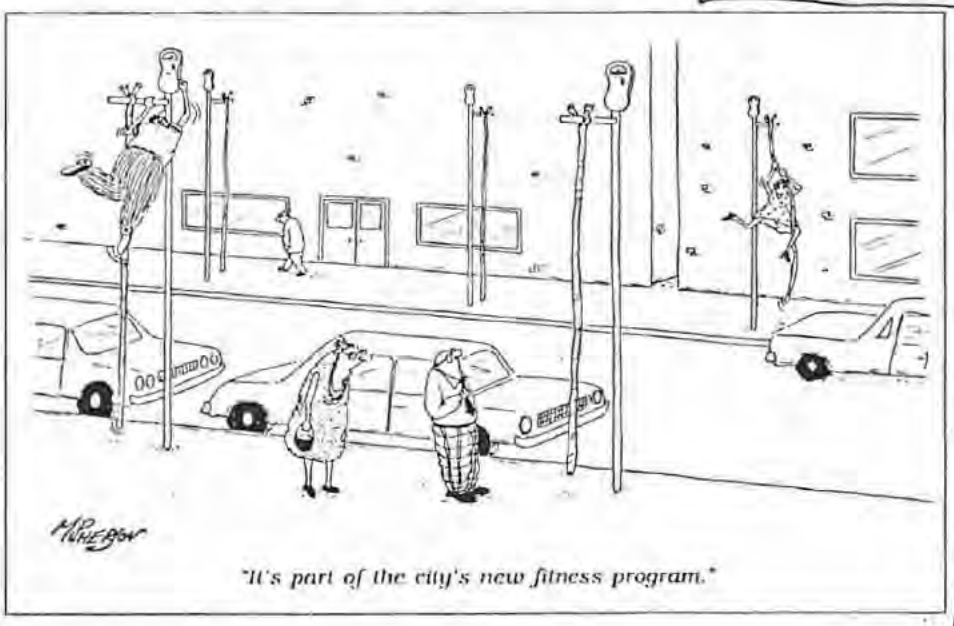
Talcum Powder Danger

It has long been suspected in the medical community that the use of talcum powder by women for sanitary purposes could increase their risk of ovarian cancer. Some recent studies have given credence to this view. Talc has been found in the ovaries of some women, due to the fact that particles can travel from the area around the vagina right up to the ovaries. Talc particles follow the same route as sperm do in reaching the ovaries.

The rationale for suspecting talc as an ovarian carcinogen derives from its chemical relation to, and natural occurrence with, asbestos, a known carcinogen. To compound the problem, one study indicated that the very real risk of ovarian cancer from talc powder was increased when spray deodorants were also used.

Further evidence for this hypothesis is seen in the case of women who have had their fallopian tubes surgically bisected for medical reasons or birth control purposes. These women show no increase in the risk of ovarian cancer due to talcum powder, because the route of transmission from the vagina to the ovary is interrupted.

More research must be done to determine the real association between talc, feminine powder deodorants, and the risk of ovarian cancer, but it is a good idea to avoid using talcum powder on sanitary napkins or around the perineum until more research is done on the subject. Other feminine hygiene products, such as the towelettes, are available that use no powder at all.



"It's part of the city's new fitness program."

Happier Feet for a Happier Body

Our feet are two of the most sophisticated and amazing structures of our bodies. Each foot has 26 bones, 30 joints, and more than 150 ligaments and muscles that keep it functioning. Supporting our weight, bal-

Date

ROUTING AND TRANSMITTAL SLIP

TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
1. Dr. Sam Shibko		
2.		
3.		
4.		
5.		

	Action		File		Note and Return
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	As Requested		For Correction		Prepare Reply
	Circulate		For Your Information		See Me
	Comment		Investigate		Signature
	Coordination		Justify		

REMARKS

Some Questions that Hiltje & I had were what to call this - DRAFT - Memo or Informal Memo.?

I have included a copy of the original Routing Slip and the original letter from (b) (6) [redacted]

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

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OPTIONAL FORM 41 (Rev. 7-76)
Prescribed by GSA
FPMR (41 CFR) 101-11.206

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Draft-Memo

Date September 14, 1992

From Standards and Monitoring Branch (HFF-156)

Subject Talc and ovarian cancer

To Mr. Harold Davis

I am providing the following information to you to assist in answering the letter that you received concerning talc. There are three issues that I can identify in this letter from Ms. (b) (6) [redacted] The first and most important is, "Whether talc is 100% safe in over-the-counter (OTC) drugs?" I do not feel that the answer to this question is within my purview. However, since talc is used in food manufacturing (as coating in chewing gums), etc.) and since studies done many years ago have shown oral use to be safe, I would think that its occasional consumption when taking OTC drugs would not be a problem. Talc that is inhaled is often cleared through the digestive system, again without any known difficulty. I would have expected to see increases in digestive system tumors if talc were to have been a problem. But as a caution, I do not know of people actually searching for talc particles in digestive system cancer samples, although it would be hard to miss such particles if they were present, even under conventional microscopy conditions.

The second issue is, "Whether there is a problem with talc's use on surgeons' gloves (the example she presents was her husband's medical record)?" There are two points to consider here. The first is that the first surgery which she mentions was done probably in the late 1950's to early 1960's. During this time period, talc was not checked for the presence of asbestos. Since then, industry has attempted to make talc for such uses asbestos-free. So the association of her husband's granuloma with "talc" may actually be an association with asbestos. How-ever, with that said, it seems from some data, that it is the particles' dimension (length versus width ratio) that is critical in the determination of carcinogenic potential. Talc can sometimes have the critical dimensions. So I would think that the association of talc with cancer risk, especially in operational situations has been greatly reduced due to modern medical practices. But that does not mean that the free use of modern, purified talc in surgical settings is recommended or totally risk free. The issue of talc and surgical gloves should be addressed by the Center for Devices.

The third issue concerns talc and ovarian cancer. At the present time, this issue as well as a review of the total regulated uses of talc is being considered by the Cancer Assessment Committee (CAC) of CFSAN. I have included here a brief summary of the findings of a majority of publications on the subject of talc and ovarian cancer. It is safe to say that this subject is of utmost importance to the FDA and will be thoroughly reviewed. There does appear to be a slightly elevated risk level (as determined by epidemiology studies) for those who use talc-based powders often as a dusting powder on the perineum. But because there are so many factors associated with this type of cancer (genetic and environmental) it would be premature for me to assume that these studies will be considered significant by the CAC. However, I have tried (in giving you these summaries) to present the picture of talc and it's association with ovarian cancer as clearly as possible. I hope that this information will be useful in answering this letter.

OVARIAN CANCER STUDIES REVIEWED

1) Henderson, et al. (1971). J Obstet Gynaecol Br Commonw. 78(3): 266-272.
- No asbestos was found in ovarian tumors, but they did find it in lung tumors, therefore the strip method works.
- Talc particles found in ovarian (75%) and cervical (50%) tumors, but cervical tumors had larger particles (up to 5μ).

2) Natow. (1986). Cutis 37(5): 328-329. (NOTE: This is a very general review with no references.)
- Talc use was associated with intra-abdominal fibrosis and granuloma. It is suggested by the author that these cancers were caused by the dusting of surgeons' gloves with talc.
- After 1972, talc is supposed to be free from asbestos.
- As little as 30 minutes after particles of talc powder have been introduced into the vagina, talc can be found in the fallopian tubes.
- Talc has been found deeply imbedded in ovarian cancer specimens.
- Habitual dusting of the perineum with talcum powder seems to be associated with a threefold increased risk of ovarian cancer.

3) Henderson et al. (1979). The Lancet. March 3, 1979, p. 499.
- Addressing several objections raised over the years since the 1971 paper (noted above) the authors show that talc is indeed found in tumor cells as well as in normal (non-malignant) tissues. They attempt to keep the samples free from glove talc and other contaminating sources, so that the talc present is that from the sample.
- They also suggest that talc use in the past has not led to cancers of the lung or the peritoneum, but it would be premature to say that it has no effects on tissues, like the ovaries, which are highly differentiated and which undergo cyclic changes due to hormonal secretions.

4) Cramer, et al. (1982). Cancer. 50: 372-376.
- An epidemiological study that found an increased risk among matched populations for ovarian cancer when talc used as dusting powder on the perineum or on sanitary napkins (relative risk 1.92) and when they used both methods the relative risk was 3.28. The authors conclude that this study supplies some support for the association of talc with ovarian cancer. They suggest that there is a similarity of ovarian cancer to mesotheliomas, and that this is due to the chemically similar nature of talc to asbestos, which causes mesotheliomas.

5) Whittemore et al. (1988). Amer J of Epidemiology. 128(6): 1228-1239.
- Case-control study where there were no statistically significant trends with increased frequency or duration of talc use- (52% of cancer patients vs 46% of controls- which included both hospitalized [non-ovarian cancer patients] and random telephone respondents matched for age, race and other criteria).
- They were not successful in making associations with timing and occurrence of hysterectomy and tubal ligations and talc use and ovarian cancer.

6) Harlow et al. (1992). Obstetrics & Gynecology. 80(1): 19-26.
- This case-control study showed a slight association between talc and ovarian cancer when talc was applied to the perineum or to undergarmets, sanitary napkins, or to diaphragms (1.5 Odds Ratio [OR]). Those who had perineum exposure of talc and used it directly as a body powder had an OR of 1.7, while those who applied it daily (1.8 OR) or who used it for more than 10 years (OR 1.6) seemed to have slightly elevated ORs. The subgroup with the highest OR (but who accounted for only 10% of the patients with ovarian tumors) were those who had made more than 10,000

applications during years when they were ovulating, and who had an intact genital tract.

- A meta-analysis of data from several other groups plus this study seems to show an OR of 1.3. for any perineal talc exposure and ovarian cancer risk.
- The authors readily admit that there are many confounding factors both in their own data and in the other studies, which make it hard to say that talc has more than a modest role to play in ovarian cancer rates. However, as they also point out, ovarian cancer survival rates are not good, so even though talc may be associated with only 10% of ovarian cancers, this knowledge might be useful in reducing the number of women dying from ovarian cancer.

7) Booth et al. (1989). British J Cancer. 50: 592-598.

- Talc questions were added later to this survey (3 months). This survey was an unmatched study. No questions were asked about how long the women had used talc, nor whether their present use reflected the past usage. There was no difference between controls and patients with regard to the use of talc on their diaphragms.
- The results show a greater relative risk for weekly talc users than daily talc users (2.0 vs 1.3). Thus the authors conclude that these results (along with others) are "...insufficient to reject an association..." between genital use of talc and ovarian cancer.

8) Harlow et al. (1989). Amer J of Epidemiology. 130(2): 390-394.

- In this case controlled study there was found to be no association between use of talc on diaphragms and ovarian cancer.
- There was a modest association (2.2 Relative Risk) between using powders containing talc when used on sanitary napkins or as a dusting powder. Those powdering the perineum with deodorizing powders had 2.8x the risk than those who did not powder at all.
- The authors believe that these results may be due to asbestos or to the deodorizing substances present in the powder, and it does not necessarily implicate the talc. Nor is this a result that is specific to just borderline tumors, as others have found similar relative risks for all ovarian tumor types.

9) Wehner et al. (1986). Fd Chem Toxic. 24(4): 329-338.

- Cynomolgus monkeys were given (30 injections into the vagina) neutron-activated talc (125 mg) in order to determine talc translocation. Samples from various tissues were analyzed for radioisotopes (four types) in order to exclude leaching of some of the label.
- These studies showed no translocation of talc from the vagina to the ovaries. There was a great deal of variation in talc levels in the vagina, due mostly to the animals menstrual cycles.
- The authors conclude that some earlier positive studies might have been due to contamination of samples. There is also some evidence that negative abdominal pressures due to the patient's position, might draw talc up to the ovaries. But normally talc would have to go against the normal flow cause by ciliary action in the oviduct epithelium.

It should be pointed out that the epidemiology studies are of variable quality, and that the conclusions of the CAC will depend upon all the data including the recent National Toxicology Program's report on talc inhalation studies with rats and mice. This information should allow you to answer the questions presented in the letter by (b) (6)

Louis J. Pribyl, Ph.D.

Meeting - 2/12/96
Talc Petition
Agenda

Components of petition

- Initial petition
- Several comments on petition, including extensive comment from CTFA

Issues

1. **Where we are on the review of the petition - Chemistry review**

a. Original Petition Letter to petitioner –

- Petition lists references to support request - no copies of references provided.

b. Comments on petition

CTFA Comment on petition

- Each study included in comment has been reviewed by CTEB and the identity (or lack of identity) of substance tested is described.

Other comments on petition - no technical information - Nothing to review

c. Background

- Identity of cosmetic talc and existing standards for talc
  - Summarized data in petition on talc. Identified existing chemical standards for talc. Identified lack of recent survey identifying cosmetic talc, that used modern methodology. Identified prior survey of talc (mid 1970's) done by FDA. Critical information necessary to assess significance of results is missing. Attempting to locate missing information.

- Prior agency actions on talc - Identified several prior actions, and docket numbers for petitions. Identified FDA's action on citizen petitions and obtained documents informing petitioner of action.

  - 1979 letter from Commissioner Kennedy to Public Citizen Health Research Group
    - check who signed off on letter

  - 1980 Citizen Petition (inhalation) (Docket No. 80P-0091)
    - Need to review docket and get copies of relevant material

  Inhalation

  Grad Student

  1983 Citizen Petition (Docket No. 83P-0404)
    - Need to review docket and get copies of relevant material – Impurities – Asbestos

  - 1990 Proposed Skin Protectant Monograph (Docket No.???
    - Need docket number and look at docket for information relating to talc; get copies of relevant material

  Copy ordered

  Published paper. William E. Gilbertson, "The Regulatory Status of Talc" Reg. Tox. and Pharm. 21, 230-232 (1995)

2. **Where are we going on the review of the petition**

a. Review of original petition

- (b) (5) [redacted]
- (b) (5) [redacted]

b. Review of CTFA Comment on petition

Chemistry

- A focussed literature search for articles on composition of talc might allow a determination whether information submitted in comment is representative of the literature, or is a biased selection from the literature.

- A conclusion regarding the validity of data in the comment on the composition of cosmetic talc would allow a better assessment of the significance of the toxicological data.

Toxicology

- Need toxicology review of each study

c. Background

- Identity of talc
  - Completion of search for missing data on prior talc survey would be useful for future considerations of talc. (b) (5) (b) (5) (b) (5)
- prior agency actions on talc
  - (b) (5)
  - (b) (5)
  - (b) (5)
  - (b) (5)

d. Final action on petition

- (b) (5)
- (b) (5)

October 30, 1996

Note To: Jason Brodsky (HFI-60)
FDA Broadcast Media Staff
Parklawn Building

From: Stanley R. Milstein, Ph.D. (HFS-101)
Special Assistant to the Director
Office of Cosmetics and Color
FDA-CFSAN

Subject: **Talc Citizen Petition**

This responds to your request this afternoon for information concerning the status of the Talc Citizen Petition, currently under review by our Office. You indicated that this information is needed, pursuant to a mass media interview being given by the petitioners. I indicated to you that I have no direct information concerning the status of the petition review or its outcome, but I recommended that, in the absence of our Office Director, Dr. John E. Bailey, you speak with Mr. Raymond L. Decker (Director, OCAC/DPEP) or Dr. Adele Dennis (Director, OCAC/DSAT). Finally, we discussed the Talc Symposium that was co-sponsored by FDA and the ISRTP (International Society for Regulatory Toxicology and Pharmacology) and I attempted to summarize for you the major issues re. the chemistry, toxicology, and epidemiology of talc that were explored at the Symposium and indicated that the proceedings from the Symposium had been published in the peer-review journal, *Regulatory Toxicology and Pharmacology* (*RTP*, **21**, 211-215 [1995]).

Accompanying this Note, you will find a copy of the Executive Summary for the published 1995 symposium on talc. It will rapidly give you an overview of the symposium's major discussion points and conclusions (such as they were). Concurrently, I have placed a full copy of the symposium in the interoffice mail, and you should receive it tomorrow. Please feel free to call on me if I can be of further assistance in providing interpretation or commentary.

Also, please advise me (as we discussed), if you should be unable to get in contact with Mr. Decker or Dr. Dennis (in Dr. Bailey's absence). Thanks.

SRMilstein
202-205-4061

cc: HFS-100 (Bailey)
HFS-105 (Decker)
HFS-125 (Dennis)

Talc & Consumer Uses + Health Perspectives
Jan. 31 - Feb 1, 1994
National Library of Medicine

Bailey, J.E.
1992 NTP inhalation study - some evidence of carcinogenicity in male rats; not female nor male/female mice

Gettings, S.D. (CTFA Director of Toxicology)
hydrous Magnesium silicate
US: 900,000 Tons/yr (6% cosmetics; 48,000 TPY)
occurrence - all continents; each deposit chemically unique
physically - stacked plates
treatment - (produces 90-95% pure talc); ground talc ground, mixed w. water; talc floats · impurities sink; water removed; talc screened thru various mesh sizes for various applications.
particle size determination - wet sedimentation; electron microscopy
application - powders, tableting (pills) ↑ coating, slip agent, antiperspirants, foods (grams)
properties - softest mineral known, sheet-like shape (slip)
Cosmetic application
① as solid matrix (antiperspirant) (4-10%) } non
② semi-solid matrix (eye shadow) (30-40%) } respirable
③ powders (99%) (Baby powder) - 200 mesh talc; fragrance retention; slip
(Note that the particle size of talc used for the NTP study far too small for cosmetic use!)

Talc + asbestos are not formed under the same conditions therefore by properly selecting mining sites, asbestos-free talc can be obtained.

Exposure: .2 - 2 mg/m³ avg. inspired dose by adults via adult use + baby diapering
- NTP study: 2000 - 20,000 times greater exposure than estimated human exposure.

Conclusion - 200 mesh talc used in powders too large to be respirable. Smaller mesh talc used in products where it is bound (antiperspirants). NTP claims talc used in rat study cosmetic grade; speaker claims no. There are some smaller particle talc present in 200 mesh talc, but levels very low.

Gilberton, W. Regulatory Status

Official definition: USP XXII / FD. Chemicals Codex, 3rd ed.
no USP particle size definition for asbestos

British Pharmacopeia - defines talc differently than USP; movement for definition harmonization.

Uses - diaper rash prevention; drugs (like anticaking agent: pills)

Fed. Register: June 1990 - talc listed Category I; GRAS; FDA proposed warning label re. avoiding inhalation. (Note CFR 347) and directions for use.

21 CFR 73 + 82: uses of talc as cosmetic coloring agent

21 CFR 700 - negative uses of talc

FDA data base: 7 baby powders, 435 powders, 665 face powders, 9 mens talc powders, 35 foot powders (note there is a voluntary registration program)

1977 - FDA study on asbestos in talc.
talc used in some devices (eg. surgical gloves, condoms)
Claims: cosmetic - soothes, smoothes, lubricates
drug - protects against diaper rash, chafing

Oberdorster, G. - Inhalation Toxicology

w. increasing dose effects go from inflammation, particle retention; increase of type II cell proliferation, benign & malignant tumor formation

"overload" - when inhalation levels are so high, clearance time of particles from the lung significantly increases (eg. from 70 days to 300 days).

the smaller the particles the longer the clearance time

no evidence for increased lung tumors in coal workers exposed to coal dust. (Exposure likely ≥ exposure to particles dust in rat inhalation study where rats were positive)

there appears to be a "threshold" dose of particle exposure below which there is no adverse effect. when exposure ≥ clearance rate, occurrence of lung fibroblasts increases & the occurrence of tumors more likely.

NTP policy - use highest tolerated dose. for inhalation study this would be 250 mg/m³ - animals would be "swimming" in the material. Recommends that 3 levels should be used, including the max. tolerated dose & a lower dose where the lung can clear the dose.

NTP Study - 3 levels tested in range finding study, 2, 6 & 18 mg/m³; impaired clearance evident at 6, & 18 mg/m³. In chronic study, tumors [illegible]

at lower dose. Conclusion - only at higher doses was "overload" level reached.

Concludes presenting lung overload in humans will also present tumors in humans.

Clearance rate in human ≈ .0015 mg/day

Boorman, G NTP Chronic Studies in Rats

max. exposure used in NTP study to determine if further studies needed because neg. test would result in no further interest. (i.e. if tested at low dose).

NIOSH requested NTP study due to worker exposure

NTP - 2 yr (duration) study; 2 exposure levels (6 mg/m³ + 18)

mice - 2 yrs., 18 mg/m³: no alteration in cancer incidence

rats - 2 yrs. - lung inflamation observed at highest dose also observed adrenal medulla neoplasm in both male + female rats at statistically significant increase over controls - don't know why.

males - no increase in tumors at any exposure levels

females - 9/50 adenomas, 5/50 carcinomas (both significantly significant above controls). 1/50 squamous cell carcinoma

no tumors at 6 mg/m³ at any dose. Concludes over-burden dose between 6-18 mg/m³.

noted that TiO_2, chrom. dioxide, volcanic ash, quartz all pos. (i.e. tumors) in female rats but not male rats.

It was suggested that a neg. dust control should have been included in the NTP study.

"Female rats uniquely sensitive to inert particles"

Suggested studies w. glass beads or plastic would be

valuable.

Does not ~~of~~ believe that adenoid tumors were associated w. talc.

Goodman, J. I. Review of NTP Chronic Rodent Studies

(Note - did not agree with the conclusion of the NTP study)

Does not agree with testing at MTD (max. tolerated dose)

Positive results of "carcinogen" to a compd - hard to get rid of label.

Other data collected during the study was not used to make conclusion (lung burden, lung capacity, lung fluid enzymes*, lung fluid cell population*, lung collagen metabolism + protein synthesis*, proteinase activity*) * females found to be more sensitive than male rats.

Conclusion - MTD level has been exceeded for female rats, therefore this level was inappropriate.

When dealing with common tumors, statistically significantly criteria should be more stringent. If this is accepted, then the incidence of female rat tumors was not significant. (Note - there was an increase in tumors in controls (spontaneous) over that observed in historically. This was neglected when formulating a conclusion from the NTP study).

"Dose influences mechanism of action"

Panel Discussion

"We are seeing in this study a non specific response in this study" (i.e. response not uniquely due to talc itself but due to air particulates generally).

Since MTD was exceeded, it is difficult for regulators to make a determination of the significance of the NTP study.

Regarding neg. controls - there aren't any known. Most talc particles in consumer products would be trapped in the nose. Finer ~~produc~~ talc particles were used in the NTP study to determine the effects on inhaled talc particles. "Talc certainly not a carcinogenic problem under typical conditions of use."

Kuschner, M. Human Relevance of Rodent Bioassay Pathology Data
Human tumors different from tumors in the rat.

Crapo, J.D. Species Differences in Lung Physiology + Toxicity
Branching (Lung) different between rodents + humans - effects where inhaled particles will interact w. cells.
Be careful extrapolating from rodent to man based on dose alone.

Weissmann, B.T. Hypothesis on tissue-induced Toxicity mechanisms in the lung
Two mechanisms proposed:
Direct interaction w. cells - interfere w. membranes + DNA formation
Indirect - cause active oxygen species to form or growth factors which in turn cause cancer
Talc has been used frequently as a neg. control for inhalation studies on silica + asbestos!

References re. talc toxicity (ie. lack of)
Kennedy, Crit. Biochem. Biophys. (1984) 365, 359
Gann, Environ. Res. (1993) 62, 28

Conclusion -

talc relatively non-mumbranolytic
talc little genotoxic potential
talc shows no cell proliferation response

Gori, G.B. Ovarian Exposure Concern

"Can we trust data which has only a 30% concordance between mice + rats?" [i.e. to extrapolate animal data to man].

"... risk is virtually nonexistent to humans."

Austin, H. Historical Review of Risk Factors in Ovarian Pathology

15 per 100k annual US incidence ovarian cancer
8 per 100k deaths per year
incidence - ranks #6 (incidence) + #4 (mortality)
trends in mortality + incidence stable since 1973
evidence indicates use of oral contraception reduces mortality late
rates highest in industrialized countries - w. Japan as the exception
incidence somewhat higher for whites than blacks
other factors which decrease cancer incidence

- oral contraception
- breast feeding
- child bearing
- hysterectomy

} all decrease ovulation frequency

(ovulation requires some tissue repair - this constant repair + cell growth somehow [illegible] ovarian cancer incidence)

Women who have any children are 1/2 risk of developing ovarian cancer than women w. none.

ovulatory age also related to risk. Early age of ovulation + late age of menopause → increased risk.

See Chen (92) Rosenblatt ('92) Tzonou ('93) for other published studies on correlation of talc use and ovarian cancer incidence.

Family history (genetic) is also a risk factor in ovarian cancer

Brown, A.L. Migration of Talc to the Ovaries

Pelvic talc can migrate to ovaries - route unknown

via vascular system - some evidence; I.P. injection in hamsters; found talc throughout body

via G.I. tract - intestinal absorbtion negligable; eliminated in feces

via urogenital tract - (Phillips study - labeled talc injected vaginally in rabbits - no talc found in ovaries).

Henderson (1971) found talc in ovarian tumors of women; Study repeated (1979) - found talc in normal ovaries of women

Comment from audience - study on translocation of talc to human ovaries in literature flawed; no controls conducted; they repeated expt. using controls + found ~~talc~~ particles (talc?) in the controls. Concluded that particles ubiquitous. Another expt: deposited neutron activated talc in the vagina; found no translocation. "How can these particles migrate upstream?" Questioned analytical techniques used by Henderson

Note that Henderson used mineralogical technique and not

a histological technique to identify talc in ovaries*

Comment: if talc moves into the body (ovaries) then other silicates would also be found (from pill coverings, binders etc).

* Talc used to be used on surgical gloves - may have contaminated the ovaries when they were removed for analysis.

Harlow, B.L. Epidemiologic studies of perineal talc exposure

Many upto from 1933-47 of talc granulomas following surgery due to talc on surgical gloves.

Historically, - women exposed to asbestos have higher risk of ovarian cancer.

However, in follow-up study - found talc in ovaries taken with forceps only (i.e. no glove used).

Overall talc / ovarian cancer association:

9 studies

2 studies showed greater risk (i.e. significantly significant)

some less risk over those not using talc.

Appears to be a significant correlation between the frequency of talc use over a lifetime and the risk of ovarian cancer.

Showed risk of ovarian cancer before 1960 greater than after 1960 - due to reduction of asbestos fibers in older talcs

Conclusion -

- only weak association between talc use + ovarian cancer

Hartge, A. P. Epidemiologic Studies (continued)

problems w. epidemiologic data:

- not scientific
- recollection of (talc) use
- distinguishing confounding factors which cause like effects
- transport - how did it get there?

Conclusions -

- no risk of using talc on diaphram
- use of talc on body may be risk
- for user of talc daily (on body) for 10 yrs, risk ranges from 1.0 (ie no increased risk) to 1.8 (ie. 80% higher risk)

Comment - Certainly a lack of data on presence of talc in ovaries. - Other minerals are very similar structurally to talc and only in the last 10 years are techniques available which can definitively measure talc in tissues.

Wynder, E. L. Significance of Epidemiology Studies

"most concern relate to metabolic overload"

6 fold increase of ovarian cancer in US vs. Japan; not so much in pre menopausal women, but in post menopausal women. (Believes this is a dietary factor) - fat intake

Rose et al. (1986) high correlation of fat intake + ovarian cancer ($R = 0.78$)

Critical of published epidemiological studies for not including information of frequency + duration of talc use.

A risk of 1.8 (i.e. 80% increased risk) can be significant in large populations.

Confounders of epi. studies include: Jewish, marital status, age, education, race, tubal ligation, oral contraception, asbestos exposure. (e.g. Jewish women use hair dyes more frequently than others). A large study ≥ 1000 women, excluding all of these cofactors.

Epi. studies have inherent bias - e.g. scientists would rather publish a positive study; most people interviewed underestimate their fat intake; if patients think exposure to talc may have something to do with their disease, they frequently think they use the product more often.

Evaluation of talc vs. ovarian cancer epi. studies

- risk low - 1.3 (but significant)
- risk between studies not consistent

Conclusion - may be relation between ovarian cancer + talc use, but additional information is needed to make a definitive conclusion.

Fleiss, J.L. Meta Analysis: Constraints in Interpretation of Epi. Studies of Perineal Talc Exposure

Synonyms: for meta analysis pooling, combining information

Definition: Procedure for combining + integrating numerical data

Panel Discussion

Bias is difficult to avoid - it is part of human nature

The increased risk of ovarian cancer due to talc use

is a hypothesis which remains to be tested."
Talc causes fibrosis, yet no fibrosis has been observed
in ovarian tissue.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date April 8, 1994

From Acting Director, Office of Cosmetics and Colors, HFS-100

Subject Follow-up to Talc Symposium

To Director, Center for Food Safety and Applied Nutrition, HFS-1

This memorandum describes the activities planned by the Office of Cosmetics and Colors (OCAC) in follow-up to the talc workshop held Jan. 31 - Feb. 1, 1994. These activities are intended to assess the scientific and medical information presented at the workshop and determine what, if any, regulatory action may be necessary. This plan will also detail any additional studies that may be necessary to resolve remaining questions about the safety of talc in FDA regulated products. OCAC will provide you with period reports on the progress made under this action plan.

The Talc Symposium provided outside expert opinion regarding two areas of concern raised regarding cosmetic use of talc:

- Inhalation toxicity as reported in the NTP chronic study in rats;
- Ovarian cancer as reported in the epidemiologic studies of perineal talc exposure (study of Harlow, Brigham and Women's Hospital; study of Hartge, National Cancer Institute)

Planned activities are as follows:

Responsible Supervisor: Dr. D. Adele Dennis (HFS-125). Manage overall project by providing guidance on individual staff responsibilities, time frames, procedure, reporting and administrative record.

1. Project manager: Dr. Robert Bronaugh (HFS-128). Compliance coordinator: Allen Halper (HFS-105). Manage and track the follow-up activities. Establish liaison with CDER and CDRH to share action plan for comment, possible collaboration and progress reports. *Timeframe:* Immediate.

2. Summary of symposium *Timeframe:* Completed. We have summary reports (Bronaugh and Yourick; Havery) regarding the conclusions and concerns raised at the symposium.

3. Identity and specifications for talc
Havery: Review the available information (including Cosmetic Ingredient Dictionary, US Pharmacopeia, Food Chemicals Codex monographs for talc, CTFA sources, etc.) to determine the identity and specifications for cosmetic grade talc. Prepare memorandum summarizing the findings. *Timeframe:* 1 month.

4. OCAC evaluation of the studies Chemistry and toxicology in-house reviews of the three primary studies. *Timeframe:* 2 months after studies are available. (Allow 1 month to complete 2 above (approx. least 3 months total)).

NTP Chronic Study
Havery: Determine physical and chemical identity of material studied; compare to cosmetic grade talc, as determined in 3 above.
Bronaugh: Review study protocol and toxicological results from study; determine relevance of study to cosmetic use of talc.

Harlow and Hartge studies
Havery: Review studies to assess identity of material as talc
Altekruse: Review studies to assess quality as epidemiology studies
Bronaugh: Review studies to evaluated toxicological results

Other relevant studies
Bronaugh: Identify other relevant studies; review as for Harlow and Hartge studies (allow additional review time for additional studies).

5. Summary of the results
Project Manager (in collaboration with compliance coordinator): Review the summaries of the symposium and the internal reviews of the studies. If necessary, determine if legal authority for cosmetics supports issuance of controlling regulations. Prepare an initial draft memorandum that summarizes these issues and recommends possible actions within that context. *Timeframe:* 1 month following completion of internal reviews of studies.

6. Discussions of possible actions
OCAC: Meet to discuss the contents of the memorandum; in particular the possible future actions with regards to cosmetic use of talc. (b) (5) [redacted] (b) (5) [redacted] *Timeframe:* 2 weeks following completion of the initial draft memorandum.

With CDER: Meet with CDER (OTC drugs); present our draft memorandum for discussion. (b) (5) [redacted] (b) (5) [redacted] *Timeframe:* 2 weeks following the OCAC internal meeting.

7. Possible additional follow-up activity - Talc survey
Havery: Survey cosmetic grade talc raw material and talc-based cosmetic products to determine physical and chemical properties of the talc used in these products. Compare to existing identity and specifications for cosmetic grade talc (see 2 above). Determine if any additional specifications are needed to assure safety of cosmetic grade talc. *Timeframe:* Uncertain. Requires preparation and approval of protocol as well as coordination for electron microscopy.

8. Follow-up action on talc
Project Manager (in collaboration with compliance coordinator): Develop and implement any necessary compliance activities identified as appropriate follow-up action. *Timeframe:* Uncertain. Will depend on nature of action and time required to complete survey in 7 above.

Estimated Timeline

Activity	Time (months)	Total time (months)
Identity/specs for cosmetic grade talc	1	1
Internal review of 3 studies	2	3(+)
Results summary/recommended action	1	4(+)
Meetings (internal + CDER)	1	5(+)
Talc survey	?	5(++)
Final action	?	5(+++)

cc: HF-1 (Merkatz)
HF-24 (Scheman)
HFD-810 (Lipnicki)
HFZ-471 (Kammula)
HFS-3 (Oliver)
HFS-22 (Elliot/Bailey)
HFS-105 (Decker/Halper)
HFS-125 (Dennis/Bronaugh/Havery)
HFS-200 (Rulis)

Prepared by:(HFS-100)JEBailey:4/1/94
Finalized:jdc:4/8/94

C T F A

THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

April 11, 1994

E. EDWARD KAVANAUGH
PRESIDENT

John Bailey, Ph.D.
Food and Drug Administration
200 C Street, S.W.
Washington, DC 20204

Dear Dr. Bailey,

Please find enclosed a copy of a manuscript, entitled Talc: Occurrence, Characterization and Consumer Applications by Zazenski et al., which we have submitted to ISRTP for publication in Regulatory Toxicology and Pharmacology.

Should you have any questions on the manuscript, or any other questions with regard to talc, please do not hesitate to contact me.

Sincerely,

Stephen D. Gettings, Ph.D., D.A.B.T.
Director, Toxicology

Enclosure

H:\sdg\talc\corresp\1994-13

1101 17TH ST., N.W., SUITE 300 WASHINGTON, D.C. 20036-4702
202.331.1770 FAX 202.331.1969
SECURING THE INDUSTRY'S FUTURE SINCE 1894

Luzenac

June 11, 2001

Via FedEx, and/or E-mail

Dr. Bernard Schwetz
Acting Commissioner - Food and Drug Administration
U. S. Department of Health and Human Services
Parklawn Bldg., Rm. 14-71
5600 Fishers Ln.
Rockville, MD 20857

Dear Dr. Schwetz:

We are writing to express our concern that an assumption that cosmetic talc used in the United States may still be contaminated with asbestos is driving the proposal to list talc not containing asbestiform fibers as a "reasonably anticipated human carcinogen" in the 10th Report on Carcinogens. While we believe the assumption is unwarranted, we wish to make clear that if there is a genuine concern that cosmetic talc used in the U.S. may be contaminated with asbestos, we would like to meet with FDA and NIEHS to discuss the specifics of those concerns and how we, Luzenac, and other companies producing and selling cosmetic talc, along with FDA, could allay those concerns through measures such as a federal standard or guideline or testing of today's cosmetic talc.

The salient background points are as follows. Two Report on Carcinogen review groups (RG1 and RG2) voted to list talc not containing asbestiform fibers as a "reasonably anticipated human carcinogen" (6 to 1 and 7 to 1, respectively). The basis for their recommendations is set out in the Draft Background Document on Talc. That document states clearly that one of the primary bases for the recommendations is an assumption that "talc" in general "may contain asbestos fibers", and therefore it is prudent to regard talc as likely to cause ovarian cancer.[1] (P. 28) That assumption was made even though the background document acknowledges that industry adopted a voluntary purity standard in 1976 which requires that cosmetic talc be free of asbestos, and even though it is clear that the ovarian cancer studies must have involved use of talc that may well have been contaminated prior to 1976. When the nomination reached the outside peer review group, the RoC Subcommittee, they took note of those two points, among others, and voted 8-2 against listing talc not containing asbestiform fibers in the 10th Report on Carcinogens.

We firmly believe the assumption that today's cosmetic talc may still be contaminated with asbestos is completely unwarranted, based on many years of testing and the demands of our customers -- an assertion we believe we and others have made clear during the Report on Carcinogens review proceedings. We also believe it is completely invalid to propose to list talc not containing asbestiform fibers based on the

[1]We do not believe there is a genuine concern regarding other potential cancer sites. We do not believe cosmetic talc poses any risk (or hazard) of lung cancer to U.S. consumers. It is our understanding that FDA, like us, regards the 1993 NTP rodent inhalation bioassay as not being relevant to real-world consumer exposures, a position that was reflected in the published consensus statement from the 1994 workshop which addressed this issue that was jointly sponsored by FDA and ISRTP and in which numerous FDA scientists participated.

Luzenac America, Inc.
8985 E. Nichols Ave., Ste. 300 • Englewood, CO 80112 USA • (800) 525-TALC (8252) • (303) 643-0451 • Fax: (303) 799-8926

assumption that such talc actually does contain asbestiform fibers. However, we remain concerned that the RG1 and RG2 reviewers, the NTP Executive Committee (which meets June 14), and ultimately the Director and the Secretary, might continue to rely on the contamination assumption and decide that talc not containing asbestiform fibers should be listed as reasonably anticipated to cause cancer. We are also concerned with the potential impact such a listing could have on the petition currently before FDA to label cosmetic talc products as potential carcinogens. Listing of cosmetic talc in the Report on Carcinogens by itself, and certainly if followed by granting of the FDA petition, would likely destroy completely the cosmetic talc industry and market in the United States in short order for no valid reason.

In view of these dire potential consequences, we have approached FDA's Office of Cosmetics and Colors with the proposition that, assuming there are genuine concerns on the part of the responsible federal agencies that modern cosmetic talc may continue to be contaminated with asbestos, we would like to discuss with FDA how those concerns can be resolved.[2] At this point, we are discussing the matter with other producers and their representatives and the Office of Cosmetics and Colors with a view to submitting a formal request for a meeting to discuss whether there is an adequate basis for FDA action, how we should formally initiate consideration of such action, options that should be discussed, how the agency's deliberative process would proceed, and agency representatives who should be involved.

Since, at this point, it does not appear feasible to organize and take any formal action prior to the NTP Executive Committee meeting on the 10th Report on Carcinogens scheduled for June 14, we wanted you and others involved with the Report on Carcinogens program and the pending FDA petition to be informed concerning these issues and developments. We want U.S. consumers and responsible federal agencies to have confidence in the safety of our products, and we reiterate that we believe that any genuine concerns regarding potential present-day contamination of cosmetic talc can be laid to rest without federal actions detrimental to the industry.

Sincerely,

Richard Zazenski

Richard J. Zazenski
Director Product Safety
Luzenac America

cc: Dr. Adele Dennis, Office of Cosmetics and Colors
Dr. William Allaben, NCTR
Dr. Kenneth Olden, NIEHS
Dr. Christopher Portier, NIEHS
NTP Executive Committee Members

[2] We may also want to discuss how the term "containing asbestiform fibers", which is essential to the Report on Carcinogens listing proposals (which differentiate talc containing asbestiform fibers from talc not containing asbestiform fibers), should be defined in a scientifically accurate manner.

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CFSAN MP

FDA
HFI-40
Rockville, MD
20857

Dear Sir or Madam

This letter is in regards to a concern that I have over advertisement that I saw in various magazines, that I find to be very deceiving to the consumer. The advertisement is for the toothpaste Arm & Hammer Extra Whitening. The opening line of is a question stating, " Want whiter teeth in just two weeks." If you look over the advertisement, both the text and visuals, you will see that it does not assert that this product will "whiten your teeth in two weeks." It also indicates that it has been "clinically proven" through tests that the baking soda formula really does make your teeth whiter. Yet how does the consumer know this for sure? These so-called tests leave the viewer feeling unsure whether anything at all has actually been tested. The consumer is left to either believe or not too believe this claim. I feel this advertisement misleads the consumer and can make an unsuspecting viewer or reader to conclude that this toothpaste really does work in two weeks.

After reading this deceiving advertisement I feel that some action should be taken. This is the reason why I am writing this letter to you. I know that if I were to use the product I would hope that it would really work in two weeks, but because of the way it is stated, I am very unsure as to whether the advertisement is being truthful. The actions that need to be taken are to either having the advertiser restate the text from a question to an actual statement or to eliminate the advertisement all together. The consumer must feel there is the truth in the advertisement, but in this case I don't believe they would. Thank you for your time, in reading this letter.

Sincerely,
(b) (6) [redacted]

(b) (6) [redacted]
05/02/01

ROUTING SLIP
GENERATED BY: HF-40
DATE: JUN 19, 2001

FDA CONTROL NUMBER: 01 3128 **TRACER #:** **OS #:**

DATE OF CORRESPONDENCE: 06/11/01 **DATE INTO FDA:** 06/19/01

TO: BERNARD A SCHWETZ HF-1

FROM: RICHARD J ZAZENSKI, LUZENAC AMERICA

SYNOPSIS: MEETING REQUEST FOR FDA. EXPRESSES CONCERN THAT AN ASSUMPTION THAT COSMETIC TALC USED IN THE U.S. MAY STILL BE CONTAMINATED WITH ASBESTOS. LUZENAC BELEIVES THE ASSUMPTION IS UNWARRANTED AND WOULD LIKE TO DISCUSS THE SPECIFICS OF THOSE CONCERNS WITH FDA.

LEAD OFFICE: HF-1 **HOME OFFICE:** HF-40

CONTACT/PHONE#: KRISTINE M MORAN 301-827-4446

COPIES: GENERAL DISTRIBUTION
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HF-10 LINDA A SUYDAM
HF-40 LAJUANA D CALDWELL
HF-40 INDYA P GORDON
HFS-1 JOSEPH A LEVITT

COORDINATION: HF-40 ANNE B CRAWFORD
HF-40 WANDA G RUSS

SIGNATURE REQUIRED:

REFERRALS FROM HF-40

ASSIGNED TO		ACTION	DUE DATE
HF-1	CRIMC	NECESSARY ACTION	
REMARKS: PLEASE ADVISE WRUSS OF DECISION.			
HF-40	CRAWFORA	PREPARE RESPONSE FOR SIGNATURE	
REMARKS: WRUSS WILL ADVISE.			

Stewart, Shearldene

From: Russ, Wanda
Sent: Thursday, June 21, 2001 11:32 AM
To: OC Invitation Reviewers; Levitt, Joseph A; Dennis, Donna A
Cc: Wheeler, Renee J; Stewart, Shearldene; Crawford, Anne
Subject: BAS Invitation Request #01-3128

Importance: High

Attached is a MEETING request for the Acting Principal Deputy Commissioner to meet with Luzenac America to discuss their concerns regarding the assumption that cosmetic talc in the U.S. may be contaminated with asbestos and it is driving the proposal to list talc not containing asbestiform fibers as a " reasonably anticipated human coarcinogen" in the 10th Report on Carcinogens. They have been in contact with our Office of Cosmetics and Colors regarding these concerns. I suggest that the CFSAN meet with them (Office of Cosmetics and Colors) as well as a senior staff person from the Center - Joe Levitt or Janice Oliver or who ever Joe may want to recommend.

Please indicate the priority for the Commissioner accepting this request:
✓ LOW ___ MEDIUM ___ HIGH

If this is important to FDA but it would be more appropriate for another Agency representative to accept in the Commissioner's place, who would you recommend?

CFSAN / OCAC and a Center-level scientific expert.

Rationale/What other information is relevant to this decision?

Joe Levitt

Please provide your input to me by COB 6/25.

Thanks,

Wanda

cc: Oliver, Dennis

0103128.pdf

ROUTING SLIP
GENERATED BY: HF-40
DATE: JUN 19, 2001

FDA CONTROL NUMBER: 01 3128 **TRACER #:** **OS #:**

DATE OF CORRESPONDENCE: 06/11/01 **DATE INTO FDA:** 06/19/01

TO: BERNARD A SCHWETZ HF-1

FROM: RICHARD J ZAZENSKI, LUZENAC AMERICA

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LEAD OFFICE: HF-1 **HOME OFFICE:** HF-40

CONTACT/PHONE#: KRISTINE M MORAN 301-827-4446

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HFS-1 JOSEPH A LEVITT

COORDINATION: HF-40 ANNE B CRAWFORD
HF-40 WANDA G RUSS

SIGNATURE REQUIRED:

REFERRALS FROM HF-40

ASSIGNED TO		ACTION	DUE DATE
HF-1	CRIMC	NECESSARY ACTION	
REMARKS: PLEASE ADVISE WRUSS OF DECISION.			
HF-40	CRAWFORA	PREPARE RESPONSE FOR SIGNATURE	
REMARKS: WRUSS WILL ADVISE.			

Luzenac

June 11, 2001

Via FedEx, and/or E-mail

Dr. Bernard Schwetz
Acting Commissioner - Food and Drug Administration
U. S. Department of Health and Human Services
Parklawn Bldg., Rm. 14-71
5600 Fishers Ln.
Rockville, MD 20857

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01-3128

assumption that such talc actually does contain asbestiform fibers. However, we remain concerned that the RG1 and RG2 reviewers, the NTP Executive Committee (which meets June 14), and ultimately the Director and the Secretary, might continue to rely on the contamination assumption and decide that talc not containing asbestiform fibers should be listed as reasonably anticipated to cause cancer. We are also concerned with the potential impact such a listing could have on the petition currently before FDA to label cosmetic talc products as potential carcinogens. Listing of cosmetic talc in the Report on Carcinogens by itself, and certainly if followed by granting of the FDA petition, would likely destroy completely the cosmetic talc industry and market in the United States in short order for no valid reason.

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Sincerely,

Richard Zazenski

Richard J. Zazenski
Director Product Safety
Luzenac America

cc: Dr. Adele Dennis, Office of Cosmetics and Colors
Dr. William Allaben, NCTR
Dr. Kenneth Olden, NIEHS
Dr. Christopher Portier, NIEHS
NTP Executive Committee Members

[2] We may also want to discuss how the term "containing asbestiform fibers", which is essential to the Report on Carcinogens listing proposals (which differentiate talc containing asbestiform fibers from talc not containing asbestiform fibers), should be defined in a scientifically accurate manner.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

HFS-125

Food and Drug Administration
Rockville MD 20857

June 29, 2001

Mr. Richard J. Zazenski
Director, Product Safety
Luzenac America, Incorporated
8985 E. Nichols Avenue
Englewood, Colorado 80112

Dear Mr. Zazenski:

Thank you for your June 11 letter requesting a meeting to discuss your concerns about cosmetic talc and asbestos fibers. While I am unable to meet with you personally, staff in the Office of Cosmetics and Colors would be pleased to arrange a meeting to address your concerns. Please contact Dr. Adele Dennis, Acting Director of the Office of Cosmetics and Colors, at 202-205-4530 to make the necessary arrangements.

Sincerely,

BA Schwetz

Bernard A. Schwetz, D.V.M., Ph.D.
Acting Principal Deputy Commissioner

docname:E:\Wp\ANNEC\zazenski013128.doc
drafted:ABCrawford:HF-40:6/28/01

cc:
HF –1 (2)
HF-40 (Russ, Crawford)
HFS-1
HFS-125 (Adele Dennis)

INCOMING

See Dennis Email E

Dennis, Donna A

From: Zazenski, Rich (LNA) [Rich.Zazenski@america.luzenac.com]
Sent: June 07, 2001 2:17 PM
To: Dennis, Donna A
Subject: Talc Specification

Dear Dr. Dennis:

By way of introduction, my name is Richard J. Zazenski, Director of Product Safety, Luzenac America, Inc. Luzenac is part of the worldwide Luzenac Group, the world's leading producer of talc products. Please visit our website at www.luzenac.com.

I have learned that Mr. Bill Kelly has recently spoken with you about talc and our (talc producers) willingness to work with the FDA to help formulate a cosmetic talc specification. I would like to call you in the next few days to discuss this issue, but let me take this opportunity to "put on the table" some of the options we would like for you to consider:

(1) Assuming talc (non-asbestiform) does not get recommended for NTP listing, we need to re-establish some degree of public confidence in cosmetic talc products. As such, perhaps the FDA might consider requiring cosmetic talc to meet the talc purity standards of USP and/or Food Chemical Codex. Discussing this potential with several other talc producers met with positive feedback.

(2) Additionally, we can discuss an asbestos specification option which requires that cosmetic talc "does not contain detectable asbestos" when analyzed via Transmission Electron Microscopy (TEM). I think we all recognize XRD, PCM, and PLM are simply not sensitive enough to provide complete assurance that the talc is free of detectable asbestos.

As you may know, we supply (b) (4) with all their cosmetic talc requirements. As such, we are required to employ strict quality control protocols in our manufacture as well as use TEM (independent lab analysis) for certification for the absence of asbestos. Although their talc specification is not specifically patterned after USP, their talc meets USP, EP and BP purity specifications. Perhaps their "high-standards" should become the "required" industry standard. If this will help re-establish public (and regulatory) confidence in the purity and safety of talc, then we would all welcome the requirement (I might also add that it is the policy of Luzenac that we will not sell talc products containing asbestos - and we do not entertain the argument advanced by others as to whether or not a particular fiber meets the "technical" definition of asbestos).

With regard to NTP, Luzenac firmly believes that the "science" does not warrant a talc (non-asbestiform) listing by NTP. We particularly object to

NTP's overt disregard of the findings from the 1994 ISRTP/FDA workshop on talc. Our "public" comments are posted on the NTP website.

Thank you for this opportunity to consider the "talc" issue. I'll try to give you a call either Friday or Monday if that is convenient.

Sincerely,

Rich Zazenski
Luzenac America
303-643-0404

FY 2001 OWH Funding Application

Part I

Principal Investigator:
Donald C. Havery
Chief, Cosmetics Technology Branch
Office of Cosmetics and Colors
HFS-127
Phone: (202) 205-4345
Fax: (202) 205-5098
Email: Dhavery@CFSAN.FDA.gov
Supervisor: Dr. D. Adele Dennis
Division Director: Dr. Sandy Bell, Acting
Office Director: Dr. D. Adele Dennis, Acting

Co-Investigator:
Stanley M. Cichowicz
Biologist
Acting chief, Microanalytical Branch
Office of Plant and Dairy Foods and Beverages
HFS-315
Phone: (202) 205-4480
Fax: 202-205-4091
Email: SCichowicz@CFSAN.FDA.gov
Supervisor/Division Director: Dr. Douglas Park
Office Director: Dr. Terry Troxell

Non-FDA Collaborators:

Organization	Names
Bain Environmental, Inc.	Laurie Bain
Bain Environmental, Inc.	Robert Schreiman

Part II

Is this project a continuation or extension of a previously/currently funded project: No

Center/ORA project #	Start date	Completion date
21956	2/1/01	2/1/02

Research involving animals: No

Research involving human subjects: No

Will a review division in FDA benefit from this project? Yes. A citizen petition was filed with the FDA in 1994 by the Cancer Prevention Coalition, requesting a warning label on talc powders such as " Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases the risk of ovarian cancer."

If yes, list Center/ORA/Office/Division: CFSAN/OCAC/DSAT

Part III

Project Title: The determination of the composition of cosmetic grade talc

Project statement: Ovarian cancer is one of the leading causes of mortality among U.S. women. Epidemiological studies have linked talc use in the perineal area with ovarian cancer (1-19). Since talc is a mined product, cosmetic grade talc is a heterogeneous material and can contain other undesirable minerals such as asbestos.

Project objectives: The proposed study will examine the composition of cosmetic grade talc, focusing on the presence of asbestos. Asbestos, a known carcinogen, can be found in talc if the mining site is not carefully selected or if the talc ore is not sufficiently purified. The asbestos concentration, of currently marketed cosmetic talc are needed to clarify the role of asbestos as a factor in the cause of ovarian cancer. The National Toxicology Program (NTP) is considering talc as a possible compound for restudy. The Cosmetic Ingredient Review (CIR) recently decided to perform a separate review of talc because of the toxicological issues relating to talc use. There are few current data available on cosmetic talc composition. The data collected in this survey will be needed in order for the agency to pursue any regulatory action in the event of adverse findings by the NTP or CIR. The data collected will also assist in addressing the citizen petition's request for a warning label on talc products.

Abstract of Research Plan: Epidemiological studies have linked talc use by females in the perineal area with ovarian cancer, one of the leading causes of death in American women. Talc and asbestos, a known carcinogen, can be found together if the talc mining site is not carefully selected or if the talc ore is not sufficiently purified. The asbestos concentration of currently marketed cosmetic talc is needed to clarify the role of asbestos as a factor in the cause of ovarian cancer. Approximately 50 cosmetic talc products will be collected throughout the U.S. at retail outlets and directly from suppliers, and will be analyzed by transmission electron microscopy. Positive findings will be confirmed by x-ray diffraction.

Methods: Approximately 50 talc products will be collected for analysis, including baby, adult, and medicated talcs. Products will be purchased in the Washington, DC metropolitan area, and by FDA field personnel at retail stores from several different areas of the U.S., and directly from suppliers. By obtaining talc products from a variety of different sources, the chances of obtaining products containing talc mined from the greatest number of geographic areas will be maximized.

Products will be analyzed for composition and asbestos by transmission electron

microscopy by Bain Environmental, Inc. Any positive asbestos results will be confirmed by x-ray diffraction by another contract laboratory to be determined at a later date.

The data obtained by the contractor will be reviewed internally by Stanley Cichowicz (OPDFB). Mr. Cichowicz has previous experience in the analysis of talc for asbestos. Dr. Nancy Hepp (OCAC) will act as a reviewer of any x-ray diffraction data collected in the event that asbestiform materials are found, and x-ray diffraction techniques are use to confirm the findings. Dr. Hepp's graduate work involved the use of x-ray diffraction.

Expected Outcomes: There are two possible outcomes to this study. If no asbestos is found in cosmetic talc, then researchers studying the causes of future cases of ovarian cancer can eliminate asbestos in talc as a causative factor. If asbestos is found, then the agency will need to open a dialog with the cosmetic industry on how to eliminate the contaminant. The agency can also consider requiring a warning label against the use of talc in the perineal area by women as requested in the 1994 citizen petition.

Timeline:

Start date: February, 2000 Completion date: February 2001

February - March	Contract development
March - June	Purchase talc products; Sample collection by FDA field personnel
July - August	Sample analysis
September	X-ray confirmation (if necessary)
January	Final Report

Part IV (a) Budget

Personnel Requirements:

Robert J. Schreiman, Laboratory Director, Bain Environmental, Inc., Chicago, IL
Electron microscopist
% Effort: 95%
Duration of effort: 200 hours
Salary: none
Fringe Benefits: none

Resources

Laboratory: $22,500 ($450/sample x 50 samples)
Cosmetic products: $700
Misc: $1,800
Total budget: $25,000

Other support:

Donald C. Havery (OCAC/CFSAN): Contract development and monitoring; talc product acquisition
Stanley Cichowicz (OPDFB/CFSAN): Microscopic data analysis
Dr. Nancy Hepp (OCAC/DSAT): X-ray diffraction data analysis

Part IV

Biographical Information

Principle investigator: Donald C. Havery; Chief, Cosmetics Technology Branch

Educational Background:
1971: University of South Florida, Tampa, FL; BS
1975, 1977-78, 1991: George Washington University, Washington, DC; Graduate courses in Advanced Organic Chemistry I & II, Quantum Mechanics, and microbiology

Research and/or Professional Experience:
- Twenty years laboratory experience on the development of analytical methods for the determination of trace level food contaminants (eg. N-nitrosamines)
- Nine years experience directing the development of analytical methods for the determination of cosmetic contaminants and raw materials.
- Forty publications and book chapters on analytical methods for the determination of compounds of toxicological interest to the agency such as N-nitroso compounds, ethyl carbamate, and fragrance and cosmetic ingredients.

Co-Investigator: Stanley M. Cichowicz, Biologist, Microanalytical Branch, Office of Plant and Dairy Foods and Beverages

Educational Background:
1968, Ohio State University, BS.
1969-1972, Cleveland State University, Graduate School.

Research and/or Professional Experience:
- Sixteen years laboratory experience in the development of analytical methods for the determination of microscopic contaminants of foods using light microscopy.
- Two years laboratory work and supervisory experience in developing methods in forensic and materials microscopy, and as a forensic document examiner using polarized light microscopy methodology and digital imaging.
- Nine years laboratory experience in supervising a special problems light microscopy laboratory and developing analytical methods for the identification and characterization of ground botanical material using polarized light microscopy.

Dr. Nancy Hepp, chemist, Colors Technology Branch

Educational Background:
1983: George Washington University, B.S.
1989: Georgetown University, Ph..D.

Research and/or Professional Experience:

- Eleven years experience in the analysis of colors and heavy metals
- Graduate work in the use of x-ray diffraction

Laurie R. Bain, Bain Environmental, Inc., (See attached resume)

Robert J. Schreiman, Bain Environmental, Inc. (See attached resume)

Signature Page for Application

Project Title: The determination of the composition of cosmetic grade talc.

Principle Investigator (PI): Donald C. Havery

Co-investigator (co-PI): Stanley M. Cichowicz

DC Havery 11/3/00
Principle Investigator/Date

Sandra Bell 11/3/00
PI's Division Director/Date

Stanley M Cichowicz 11/3/00
Co-investigator/Date

for DLP 11/3/2000
Co-PI's Division Director/Date

Bain Environmental, Inc.

LAURIE R. BAIN
BAIN ENVIRONMENTAL, INC.
(b) (6) [redacted]

Management professional with 14 years of experience in environmental consulting, field and analytical services complementing previous regulatory compliance and safety experience.

EDUCATION

1987-1988 M.S., Occupational Safety Management, Indiana State University, Terre Haute, Indiana (GPA 3.8/4.0)
Graduate research: The comparison of the Fibrous Aerosol Monitor with NIOSH Method 7400 and also a comparison of the K^2 Asbestest with polarized light microscopy for the detection of asbestos.
Honors: Academic Scholarship and Student Assistantship

1981-1985 B.S., Southern Illinois University, Carbondale, Illinois (GPA 3.5/4.0)
Honors: Dean's list

EXPERIENCE

1996-Present **Bain Environmental, Inc.**
Chicago, Illinois

- Comprehensive range of services includes environmental site assessments (Phase I, II, and III); indoor air quality investigations; industrial hygiene surveys, sampling, and analyses; inspections, sampling, and analyses for lead, radon, and asbestos; and underground storage tank investigations.

1988-1996 **McCrone Environmental Services, Inc.**
Westmont, Illinois

- Responsible for compliance with federal, state and local environmental regulations regarding air, water, and solid waste.
- Developed all technical services related to industrial hygiene sampling, environmental site assessments and associated remedial activities, underground storage tanks, lead, radon, and health/safety audits.
- Conducted Phase I, II and III environmental site assessments.
- Conducted several of the largest indoor air quality investigations in the Chicagoland area.
- Responsible for the training and management of all technical personnel.
- Development, maintenance and compliance of the corporate Chemical Hygiene Plan, Hazard Communication Program and Radiation Safety Program.
- Chemical Hygiene Officer for The McCrone Group.
- Assistant Radiation Safety Officer for The McCrone Group.
- Quality Control Officer for the Good Laboratory Practices (GLP) Program.
- Responsible for maintaining and upgrading procedures and the continuous monitoring of the QA/QC Program.
- Management and oversight of AIHA, PAT and AAR Programs for laboratory and Personnel accreditations.

(b) (6) [redacted] Phone: (b) (6) [redacted] Fax: (b) (6) [redacted]

1987 **Illinois Department of Public Health**
Springfield, Illinois
- Conducting compliance inspections of asbestos abatement projects.
- Inspecting schools for asbestos-containing materials.
- Compiling data analyses and evaluating inspection reports via hazard analysis to determine required corrective action.
- Responding to variance requests in accordance with state regulations.
- Assisting in the revision of the Asbestos Abatement Rules and Regulations for Illinois Public and Private Schools.
- Testing of asbestos workers for licensure.

1985-1986 **Adams County Health Department**
Quincy, Illinois
- Performed inspections of food service establishments to determine compliance with State regulations.
- Inspected and evaluated private sewage disposal and water supply installations.
- Investigated complaints concerning the protection of public health.

PROFESSIONAL CERTIFICATIONS

- Northwestern University, "Radiation Safety," 1995.
- Midwest Center for Occupational Health & Safety, "Conducting Indoor Air Quality Investigations," 1992.
- University of Illinois, "40 Hour General Site Worker Program," 1992.
- University of Illinois, "40 Hour Hazardous Waste Site Supervisor," 1992.
- Georgia Institute of Technology, "Management of Underground Storage Tank Systems," 1992.
- The Environmental Institute, "Lead Abatement: Commercial and Industrial," 1991.
- Midwest Asbestos Information Center, "Building Inspection," 1987.
- Midwest Asbestos Information Center, "Management Planning," 1987.
- The Center for Professional Advancement, "Environmental Compliance Audits and Site Assessments," 1989.
- Air Sampling Professional - Illinois Department of Public Health, 1989.
- Asbestos Project Manager - Illinois Department of Public Health, 1989.
- Asbestos Inspector - Illinois Department of Public Health, 1989.
- Asbestos Management Planner - Illinois Department of Public Health, 1989.
- Midwest Asbestos Information Center, "Operations and Maintenance," 1987.
- National Institute for Occupational Safety and Health "Sampling and Evaluating Airborne Asbestos Dust (NIOSH 582)," 1987.
- Midwest Asbestos Information Center, "Practices and Procedures in Asbestos Control," 1987.

PROFESSIONAL AFFILIATIONS

American Society of Heating Refrigeration and Air-conditioning Engineers
American Chemical Society
American Industrial Hygiene Association
American Society of Safety Engineers
Environmental Information Association
National Environmental Health Association
Illinois Public Health Association
Illinois Environmental Health Association

Robert J. Schreiman

e-mail:(b) (6) Hmpg:http://members.dsl.telocity.com/~fishman

Professional Objective

- Apply Post Graduate database management, webpage design and computer language skills
- Gain further knowledge and understanding of practical uses for different computer languages

Summary of Qualifications

Post Graduate level development experience and basic practical working knowledge of Microsoft Visual Basic 5.0, Microsoft Access 97, Microsoft Excel 97, Borland C++, Adobe PageMill 3.0, HTML Assistant Pro Lite (Web Page Construction Kit), Corel Draw 4. Personal Hardware Installation/Hardware System information and experience: Installation of US-Robotics 56K modem, Telocity DSL Modem, I-omega 100 I-omega 100 megabite Zip Drive, Hewlett Packard Scan Jet 4c, Western Digital 2.1 Gig Hard drive, 2 x 16 Megs of Ram, Sony Spressa Cd burner. All items used for the Expedition of Web Page Design.

Past Work Experience

Director of Asbestos Department May, 1997 to Present

Stat Analysis Corporation, Chicago, Ill.

Duties includ all technical aspects of the laboratory which include selection, utilizing, trouble shooting and maintaining all equipment, maintaining and upgrading procedures for analysis, coordinating intra- and inter-laboratory projects with outside firms and marketing services. Responsibilities also include continuous monitoring of the quality Assurance/Quality Control program.

Director of Laboratory Services July, 1993 to August, 1996 Carnow, Conibear Associates, Ltd. Chicago, Ill.

Duties included all technical aspects of the laboratory which include selection, utilizing, trouble shooting and maintaining all equipment, maintaining and upgrading procedures for analysis, coordinating intra- and inter-laboratory projects with outside firms and marketing services. Responsibilities also include continuous monitoring of the quality Assurance/Quality Control program.

Microscopist May 1990 to July 1993 Carnow, Conibear Associates, Ltd. Chicago, Ill.

Responsible for microscopical identification of asbestos using both transmission electron microscopy and polarized light microscopy. Also used phase contrast microscopy to analyze air samples to determine the presence and concentration of air contaminants. These responsibilities all follow with quality assurance practices, maintenance of instrumentation and training of personnel. Other duties include secondary on site field consultant for environmental and industrial health and hygiene.

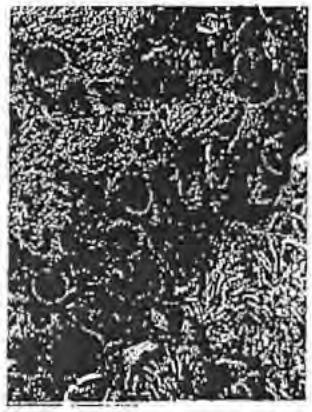
Analytical Chemist October, 1992 to July 1993 Athena Analytical Laboratory, Inc. Chicago, Ill.

Responsible for mass spectrophotometry interpretation; method development; trouble shooting of ICP, GC/MS, GC, and Spec 20 instrumentation; environmental data review; and CLP SW846, air, soil, and water analysis. Routine wet chemistry techniques included, semi-volatile extraction's, volatile organic extraction's, and metal digestion.

Analyst January, 1989 to May 1990 Aries Environmental Services, Ltd. Bativia, Ill

Responsible for transmission electron microscopy analysis including the coordination of sample preparation, microscopic analysis, quality assurance practices, maintenance of instrumentation and training of personnel. Other analytical techniques included phase contrast microscopy and polarized light microscopy. Also participated in air monitoring for determining the presence and concentration of air contaminants.

Education



Bachelor of Science, Biology, 1988 Northern Illinois University Dekalb, Illinois

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Continuing Education and Professional Training

EPA 8240 8270 Assist, 1992 Hewlett Packard Analytical Products Group, Chicago, Illinois

HP-MS Dos Operation, 1992 Hewlett Packard Analytical Products Group, Chicago, Illinois

Building Chromatography Skills, 1993 J&W Scientific, Lisle, Illinois

Atomic Emission Spectrophotometry, 1993 Perk Elmer, Oak Brook, Illinois

Hazardous Materials Safety Training Program, 1990-1992 Carnow, Conibear Associated, Ltd. Chicago, Illinois

Asbestos Identification, 1990 McCrone Research Institute, Chicago, Illinois

Niosh 582, 1990 Morgan Environmental Association, Chicago, Illinois

Transmission Electron Microscopy, 1989 JEOL, Peabody, Massachusetts

Practices and Procedures in Asbestos Control, 1989 University of Illinois, Chicago, Illinois

Biological Electron Microscopy, 1988 Northern Illinois University, DeKalb, Illinois

Professional Certification and Licensure

EPA 8240 EPA 8279 Assist, 1992

Atomic Emission Spectrophotometry, 1993

Gas Chromatography, 1993

Transmission Electron Microscopy, Illinois, 1988-1996

Air Sampling Professional, 1991, 1992

Project Management, 1991-1995

Management Planner, 1991, 1992

Research Experience

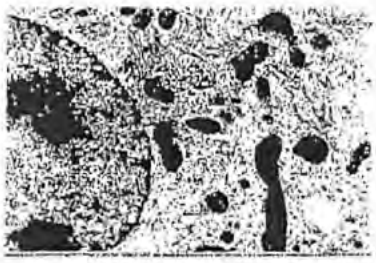
Drake University, Desmoines, Iowa, 1990-1991 Ichthyological Survey of the Fish Populations in Kalimantan (Borneo), Indonesia

Northern Illinois University, Dekalb, Illinois, Fall 1987-1988 Identification and Cultivation of Invertebrate Zooplankton

Northern Illinois University, Dekalb, Illinois, 1987-1988 Transmission Electron Microscopical examination of the inter-cellular, ultrastructural changes during the Autumnal Senescence of Maple Leaves.

Northern Illinois University, Dekalb, Illinois, Intercession Spring and Summer 1987 Examination of Plant Ecosystem Diversity of the Chichiuan Desert.

Professional Organization Memberships and Affiliations



State Microscopical Society of Illinois, 1990-1992, 1996

American Chemical Society, 1993

Midwest Society of Electron Microscopists, 1988-1992

References

1. Chang, S., Risch, H.A., Perineal talc exposure and risk of ovarian carcinoma, Cancer (1997) 79(12), 2396-2401

2. Cook, L.S., Kamb, M.L., Weiss, N.S., Perineal powder exposure and the risk of ovarian cancer, Am. J. Epidemiology (1997) 145(5), 459-465

3. Cramer DW., Perineal talc exposure and subsequent epithelial ovarian cancer: A case-control study, Obstet. Gynecol. 94(1):160, 1999 Jul.

4. Cramer, D.W., Welch, W.R., Scully, R.E., Ovarian cancer and talc, Cancer (1982) 50, 372-376

5. Cramer DW. Liberman RF. Titus-Ernstoff L. Welch WR. Greenberg ER. Baron JA. Harlow BL., Genital talc exposure and risk of ovarian cancer, Int. J. Cancer. 81(3):351-356, 1999 May 5

6. Gertig, DM; Hunter, DJ; Cramer, DW, et al., Prospective study of talc use and ovarian cancer, J Nat Cancer Inst, 92: (3) 249-252 FEB 2 2000

7. Harlow, B.L., Hartge, P.A., A review of perineal talc exposure and risk of ovarian cancer, Regulat. Toxicol. Pharmacol. (1995) 21, 254-260

8. Harlow, B.L., Cramer, D.W., Bell, D.A., Welch, W.R., Perineal exposure to talc and ovarian cancer risk, Obstetrics & Gynecology (1992) 80(1), 19-26

9. Hartge, P., Hoover, R., Lesher, L.P., McGowan, L., Talc and ovarian cancer, J. Am. Med. Assoc. (1983) 250(14), 1844

10. Heller, D.S., Gordon, R.E., Katz, N., Correlation of asbestos fiber burdens in fallopian tubes and ovarian tissue, Am. J. Obstet. Gynecol. (2000) 181(2), 346-347

11. Heller, D.S., Westhoff, C., Gordon, R.E., Katz, N., The relationship between perineal cosmetic talc usage and ovarian talc particle burden, Am. J. Obstetrics Gynecol. (1996) 174(5), 1507-1510

12. Kasper, C.S., Chandler Jr., P.J., Possible morbidity in women from talc on condoms, J. Am. Med. Assoc. (1995) 273(11), 846-847

13. Muscat, J.E., Wynder, E.L., Perineal powder exposure and the risk of ovarian cancer, Am. J. Epidemiol. (1997) 146(9), 786

14. Risch, H.A., Marrtee, L.D., Jain, M., Howe, G.R., Differences in risk factors for epithelial ovarian cancer by histologic type: results of a case-control study, Am. J. Epidemiol.

(1996) 144, 363-372

15. Rosenblatt, K.A., Szklo, M., Rosenshein, N.B., Mineral fiber exposure and the development of ovarian cancer, Gynecol. Oncol. (1992) 45, 20-25

16. Tortolero, G., Mitchell, M.F., The epidemiology of ovarian cancer, J. Cell. Biochem. (1995) Suppl 23, 200-207

17. Wehner, A.P., Is cosmetic talc safe? , Comments Toxicol. (1998) 6(5), 357-366

18. Whysner, J., Mohan, M., Perineal application of talc and cornstarch powders: Evaluation of ovarian cancer risk, Am. J. Obstet. Gynecol. (2000) 182(3), 720-724

19. Wong C. Hempling RE. Piver MS. Natarajan N. Mettlin CJ., Perineal talc exposure and subsequent epithelial ovarian cancer: A case-control study, Obstet. Gynecol. 93(3):372-376, 1999 Mar.

December 20, 1996

Chief, Cosmetics Technology Branch (HFS-127)

Response to reviewer's comments; Office of Women's Health talc proposal

Nutrition Strategic Manager (HFS-019)

The following is in response to comments made by reviewers of the proposal submitted to the Office of Women's Health entitled Survey of Cosmetic Talc for Asbestos, Composition, and Particle Size:

1. **Interpretation of results**: The PI has no experience with microscopy or asbestos analysis in talc except that acquired from reading the relevant literature in preparation of the proposal. The panel needs to be aware that the opinions expressed in the literature on the best techniques for the proposed study are not unanimous; this is a very controversial subject. The PI will rely primarily on the views expressed in the current literature and on the expertise and experience of the contractor. The contractor will collect and interpret the data, and statistically evaluate the results. The data obtained by the contractor will also be reviewed internally by Dr. Nancy Hepp (Office of Cosmetics and Colors) who has knowledge of x-ray techniques used for elemental composition, and by Dr. Ben Tall (Office of Special Research Skills) who has experience with electron microscopy.

2. **Cost of the proposed work**: The cost of the work was estimated following discussions with a potential contractor on the types of analytical methods which would be required to obtain the desired information, and the cost of these analyses per sample. Cost factors are based on the usual per-sample fees charged by the contractor for the desired analytical tests, and an estimate of the cost of commercial talc products. It was assumed that the cost estimate provided by the potential contractor was total cost, including any overhead costs. It should be noted that the analysis of talc for asbestos involves a series of instrumental techniques, and that a negitive finding by an initial test means that further analysis by other instrumental methods is unnecessary. Therefore it was assumed that most talc products would require the more costly electron microscopic analysis. If this is not the case, then additional talc products will be purchased and analyzed until the money appropriated for the study are exhausted.

3. **Ethnicity as a factor in ovarian cancer**: The statement made in the proposal relating to environmental factors as causative factors of ovarian cancer was the conclusion of the author in the cited reference (copy attached). The relationship between ethnicity and ovarian cancer was not discussed by the author of this paper. I have no additional information relating to the role of ethnic background, talc use, and ovarian cancer, and therefore cannot make any additional comments.

4. **Benchmark time frames**: Additional time frames have been added in the "Projected Outcomes" section. More specific time frames were omitted in the original proposal because a potential contractor consulted on time needed for analysis indicated that much of the analyses were automated, and analysis of 50 samples would not require a significant amount of time once the products were received.

5. **PI experience in contract monitoring**: The PI has no experience writing or monitoring a contract; however, the PI has completed contract monitoring training and has participated in the contract monitoring process as part of a Program Advisory Group (PAG).

Donald C. Havery

cc:
HFS-100 (Bailey)
HFS-125 (Dennis)
HFS-127 (Havery) ✓

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Donald Havery
Center for Food Safety & Applied Nutrition
Office of Cosmetics and Colors
Chief, Cosmetics Technology Branch, HFS-127
200 C Street SW, Room 3864
Washington, DC 20204

MAR 13 2001

Dear Mr. Havery:

Thank you for participating in the Office of Women's Health (OWH) FY 2000 Science Program. OWH received many excellent proposals this year and based on the project's scientific merit and consistency with the mission of this Office only a limited number of those proposals submitted were funded.

As we discussed, we intended to fund your proposal under our special funding initiatives program. However, we understand that new information has become available that is relevant to your proposal and this needs to be considered prior to the initiation of the project as described. Therefore, we are not funding your proposal in FY 2001. We will re-examined the overall project objectives in FY 2002 should you determined that this issue still needs to be examined. We recommend (b) (5) [redacted]

A copy of the comments made by the external reviewers is being forwarded to you. If you have other comments or questions please do not hesitate to contact Kennerly K. Chapman, OWH, at 301-827-0293.

We appreciate the time and effort taken to submit your proposal to OWH and to your interest in women's health issues. We look forward to working with you on other women's health projects in the future.

Sincerely,

Margaret Ann Miller

Margaret Ann Miller, Ph.D., DABT
Science Program Manager
Office of Women's Health

cc: Center Liaison/Blakely, S (HFS-019)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

October 18, 2000

Dr. Laurie Bain
Bain Environmental
5315 N. Clark St.
Chicago, IL 60640

Dr. Bain,

Thank you for your interest in our project on cosmetic talc composition. The purpose of the project is to determine the composition of current market cosmetic talc, determine if asbestifom materials are present, and to measure particle size distribution of the products. If our project is funded, we intend to collect up to 50 samples of commercial talc powders for analysis. A decision on what projects will be funded will be made in January, 2001.

In order for me to apply for project funding, I need the information below from you to include in my proposal. Thank you for taking the time to respond. If you have any questions or need clarifications you can reach me at (202) 205-4345, or at Dhavery@CFSAN.FDA.gov.

Donald C. Havery
Food and Drug Administration
Office of Cosmetics and Colors
200 C. St., SW
Washington, DC 20204

(b) (5)

February 4, 1994

Chief, Cosmetics Technology Branch (HFS-127)

Summary of Talc Symposium: Consumer Uses and Health Perspectives

Adele Dennis
Director, Division of Science and Applied Technology
(HFS-125)

Talc Inhalation Studies

Talc: hydrous magnesium silicate; 900,000 tons/year used in the US; 48,000 tons/yr (6%) in cosmetics. Treatment of raw talc for cosmetic use results in 90-95% pure talc. Uses: powders, antiperspirants, pill coatings/fillers, foods (chewing gum/anticaking), medical devices (surgical glove/condom coating; Note: no longer used in surgical gloves). Cosmetic uses: antiperspirants, semi-solid matrices (eye shadow), powders. Talc used in powders is 200 mesh and is the only cosmetically used talc which has the potential for being inhaled. This particle size is too large to be respirable however. Most talc particles in powders will be trapped in the nose. Talc and asbestos materials are not formed under the same geologic conditions, therefore careful selection of mining sites results is asbestos-free talc. Estimated human exposure via respiration when using powder during baby diapering: 0.2 - 2 mg/m^3.

NTP study: Requested by NIOSH due to worker exposure. Talc particles smaller than typically used in cosmetic products were used in the NTP study to determine the effects on inhalation. Larger particles would not have made it into the lungs. Two year study; exposure levels tested in chronic study: 6, 18 mg/m^3. Rodent exposure 2,000 - 20,000 times greater than estimated human exposure. Tumors formed only in female rats at the highest dose. The species of female rats used are known to be particularly sensitive to particulates. No tumors were observed in male or female mice. Adrenal medulla neoplasms were also observed in rats; origin is unknown. Talc exposure tested at the highest level was an "overload"; clearance time from the lung at this concentration is greatly increased. The smaller the particles the longer the clearance time. In a related study, there was no evidence for increased incidence of lung tumors in coal mine workers exposed to coal dust whose estimated exposure was greater than the exposure to particles in the talc rat study. TiO_2, chromium dioxide, volcanic ash and quartz dust have all produced tumors in female rats (not male rats), by inhalation. A negative dust control was not included in the NTP study which raises the question: did the observed tumors result from talc or would they have arisen from any particulate? There was one member of the NTP review panel who did not agree with the conclusions prepared by the study team. This person's comments included: (1) the maximum tolerated dose was exceeded at 18 mg/m^3, and was therefore inappropriate; (2)

there was an increase in tumors in the controls over that observed historically for this animal which was neglected in the study conclusions. Historically, talc has been used as the negative control for inhalation studies on silica and asbestos.

Caution was urged when extrapolating the rodent study results to man. Lung branching between rodents and man is different and this will effect which cells are exposed to particulates.

Ovarian Cancer and Talc Use

US annual incidence of ovarian cancer: 15 per 100,000; 8 per 100,000 deaths per year. Trends in mortality and incidence of ovarian cancer have been stable for 20 years. Factors which decrease incidence: use of oral contraceptives, breast feeding, child bearing, hysterectomy. (ie. Activities which reduce the number of times the ovary has to repair itself following release of an egg).

Talc can migrate to the ovaries, though the route is presently unknown. There is some evidence that particulates can migrate to other body tissues via the vascular system. Intestinal absorption is negligible. Radiolabeled talc injected vaginally into rabbits did not migrate to the ovaries.

Questions about talc migration to ovaries originated with a study published by Henderson in 1971 in which talc was found in human ovaries. The study was repeated in 1979 and talc was again found, this time in the ovaries of nontumoragenic women. These studies may have been flawed. Controls may not have been adequately conducted. In another experiment, labeled talc was deposited in the vagina but no translocation to the ovaries was detected. Analytical techniques used by Henderson to determine talc were questioned. Since many minerals are structurally similar, misidentification was likely. Only in the last ten years have methods become available for reliable talc measurement. Mineralogical methods were used to measure talc particulates and not histological techniques. Ovary tissues may have been removed by physicians using gloves contaminated with talc (though in the second study, ovarian tissue was removed with forceps only). Talc granulomas following surgery due to talc on gloves has been reported, but no granulomas were reported in Henderson's studies, raising questions about what particulates Henderson actually observed.

There have been 9 epidemiological studies of the relationship between talc use and ovarian cancer. Two studies showed a statistically significant increase in cancer incidence, the other studies showed a negative correlation. The risk of ovarian cancer prior to 1960 was greater than after 1960. This could be due to the reduction of asbestos fibers in talc due to modern processing techniques. Epidemiological studies suggest a small risk of ovarian cancer for talc

Talc: *(Purpose: As a follow-up to the 1994 talc symposium, to identify the chemical composition of talc, and to evaluate the identity of the material used in the NTP study on the carcinogenicity of talc particles in mice)* F. Hurley continued writing up a review of CTFA's comments to the citizen's petition relating to talc. A copy of the petition itself was obtained for review.

N-Nitrosamines: D. Havery, R. Yates, and H. Chou continued worked on a malfunctioning Thermal Energy Analyzer instrument used for N-nitrosamine analysis. It was determined that the photomultiplier tube had cracked and was bad. Fortunately we have a spare, since a new tube costs $2,000.

Other: R. Yates drafted an annual report on the activities of this project in FY95.

D. Havery drafted a letter to a scientist in The Netherlands in response to a request for a sample of 2-ethylhexyl 4-(N-nitroso-N-methylamino) benzoate. The letter was finalized. and the sample was mailed.

G. Black continued working on the inventory of CTEB's chemicals and cosmetic raw materials.

Manuscript Status: (Status changes indicated in bold type)

Accepted by the Journal:

"Determination of 2-Ethylhexyl 4-(N-methyl-N-nitrosamino) Benzoate in Commercial Sunscreens and Cosmetic Products" (Galley reviewed; publication scheduled for the November/December issue)

Under review by Technical Editing:

"Nitro musks in fragrance products - An update of FDA findings"

Under Review at the Branch level:

"A Rapid Method for the Determination of Nitrosating Agents in Cosmetic Products by Chemiluminescence Detection of Nitric Oxide"

"Determination of Formaldehyde Donating and Paraben Preservatives in Cosmetic Products by Solid Phase Extraction"

"Surveys of Commercial Fragrance Products from 1985-1992 for Nitro Musks"

"Determination of musk ambrette, musk xylol, and musk ketone in fragrance products by capillary gas chromatography with electron capture detection"

users: 1.3 relative risk where 1.0 is equivalent to no risk. There are a number of confounders which will influence epidemiological studies including race, marital status, age, education, history of tubal ligation, use of oral contraceptives, and asbestos exposure. Inherent bias of epidemiological studies were also mentioned including inaccurate interview information (eg. recollection).

A six fold increase in ovarian cancer has been identified between women in the U.S. and Japan. This may be attributed to dietary fat intake.

General Conclusion: Additional information is needed to make a definitive conclusion about talc use and ovarian cancer. Presently the increased risk of ovarian cancer due to talc exposure is a hypothesis which remains to be tested.

Donald C. Havery

"Determination of 1,4-dioxane in ethoxylated cosmetic raw materials and in cosmetic finished products"

"Determination of contaminants in fatty acid diethanolamides"

10/25/05

Bailey, Catherine J

OWH -05- statement 102505.

From: Bailey, Catherine J
Sent: Tuesday, October 25, 2005 1:40 PM
To: Obias-Manno, Dulce *
Cc: Miller, Margaret; Bronaugh, Robert L; Yourick, Jeffrey J; Katz, Linda
Subject: RE: ** Manuscript OWH** pls review for accuracy

Thanks for the opportunity to comment. See the attached version w/ tracked changes. Drs. Bronaugh and Yourick reviewed it. (b) (5) We also suggest some additional changes. Let me know if you have any questions or want to discuss.

see attached

-----Original Message-----
From: Obias-Manno, Dulce *
Sent: Monday, October 24, 2005 10:30 AM
To: Bailey, Catherine J
Cc: 'Miller, Margaret'
Subject: ** Manuscript OWH** pls review for accuracy

(b) (5)

Women rely on cosmetic products to maintain a healthy and youthful appearance and certain formulations (retinol, estrogenic hormone constituents or placental extract) may be absorbed and metabolized. In a pilot study funded by OWH on absorption and metabolism of retinol in cosmetic formulations, examined both fuzzy rat and human skin.[50] The results showed that retinol was not absorped through human skin. In a related study, several in vivo bioassays were employed to determine the estrogenic activity in different cosmetic formulations. No estrogenic activity was found in those products formulated with wild yam, and placental extract but some activity was noted in formulation containing black cohosh, glycrrhia urlensis/isoflavone complex, dong quai and wild yam. (b) (5)

(b) (5)

References:

50. Jung, C.T., Bronaugh, R.L. and Yourick J. J.: Percutaneous absorption and metabolism of retinol in fuzzy rat and human skin. AAPS PharmSci, 4(4):Abstract # R6078, 2002.

Dulce Obias-Manno, BSN,MHSA,RN
ORISE Fellow
FDA/OC/Office of Women's Health
5600 Fisher's Lane Rm 16-65
Rockville, MD 20857
Tel: 301-827-9101

Bailey, Catherine J

From: Obias-Manno, Dulce *
Sent: Monday, October 24, 2005 10:30 AM
To: Bailey, Catherine J
Cc: 'Miller, Margaret'
Subject: pls review for accuracy

(b) (5) [redacted]

Women rely on cosmetic products to maintain a healthy and youthful appearance and certain formulations (retinol, estrogenic hormone constituents or placental extract) may be absorbed and metabolized. In a pilot study funded by OWH on absorption and metabolism of retinol in cosmetic formulations, examined both fuzzy rat and human skin.[50] The results showed that retinol was not absorped through human skin. In a related study, several in vivo bioassays were employed to determine the estrogenic activity in different cosmetic formulations. No estrogenic activity was found in those products formulated with wild yam, and placental extract but some activity was noted in formulation containing black cohosh, glycrrhia urlensis/isoflavone complex, dong quai and wild yam. (R. Bronaugh, personal communication

(b) (5) [redacted]

References:

50. Jung, C.T., Bronaugh, R.L. and Yourick J. J.: Percutaneous absorption and metabolism of retinol in fuzzy rat and human skin. AAPS PharmSci, 4(4):Abstract # R6078, 2002.

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Wolf - 05 - Statement 2 102505 .doc

(b) (5)

[redacted]

(b) (5)

[redacted]

References:

50. Jung, C.T., Bronaugh, R.L. and Yourick J. J.: Percutaneous absorption and metabolism of retinol in fuzzy rat and human skin. AAPS PharmSci, 4(4):Abstract # R6078, 2002.

Dr. Bronaugh, I do not have a reference for 51. Please update if one has been accepted for publication. Otherwise, I will reference as personal communication from you.

(b) (5)

[redacted]

Food and Drug Administration
Center for Food Safety and Applied Nutrition

PROPOSAL SIGNATURE PAGE

Project Title: Survey of Cosmetic Talc for Asbestos, Composition, and Particle Size

Donald C. Hovey Principal Investigator	11/19/96 Date

CFSAN APPROVAL:

Norma A Dennis Director, Division of Science and Applied Technology	11/19/96 Date
[signature] Director, Office of Cosmetics and Colors	11/19/96 Date
Research Strategic Manager	Date
Women's Health Liaison or Appropriate Strategic Manager	Date
Research Involving Human Subjects Committee (RIHSC) Representative and/or Institutional Animal Care and Use Committee (IACUC) Chairperson ☐ N/A or *check two* ⇒ ☐RIHSC ☐IACUC *** ☐Submitted ☐Approved ☐Disapproved	Date
Director, Division of Planning and Financial Management	Date
Deputy Director for Programs	Date
Director, Center for Food Safety and Applied Nutrition	Date

November 19, 1996

OFFICE OF WOMEN'S HEALTH FDA INTRAMURAL PROGRAM

(b) (5) [redacted]

Principle Applicant:
Donald C. Havery, BS
Chief, Cosmetics Technology Branch
Office of Cosmetics and Colors, CFSAN, HFS-127
200 C. St., SW
Washington, DC 20204
PROFS ID: DCH
Phone: (202) 205-4345
Fax: (202) 205-5098

DESCRIPTION

Abstract

Epidemiological studies have linked talc use in the perineal area with ovarian cancer, one of the leading causes of death in American women. Talc and asbestos, a known carcinogen, can be found together if the talc mining site is not carefully selected or if the talc ore is not sufficiently purified. The only survey of US talc for composition and fibrous material such as asbestos using modern, reliable electron microscopic techniques was conducted twenty years ago, and asbestos was found. The composition of current market cosmetic talc, asbestos concentration, and particle size distribution are needed to assist in the evaluation of a citizen petition, and to provide data to clarify the role of asbestos as a factor in the cause of ovarian cancer.

Background

Ovarian cancer is a pernicious disease and one of the leading causes of mortality among U.S. women. An annual incidence of 22,000 new cases of cancer of the ovary have been reported, resulting in 13,300 deaths per year and an average lifetime risk of 1 in 70[1]. The highest incidence of ovarian malignancy occurs in industrialized countries of Northern Europe and North America, which points strongly to environmental factors as causative agents in the initiation of the disease[2].

Epidemiological studies have been conducted in an attempt to identify risk factors associated with ovarian cancer. Several studies have found a higher risk of ovarian cancer in women using talc in the perineal area especially in women with a long history of talc use[3-9]. The actual causes of ovarian cancer are unknown. The possibility that asbestos may be a factor has been suggested. The factors linking talc use, asbestos, and ovarian cancer can be summarized as follows: (1) talc and asbestos are chemically similar and can occur naturally together depending on mining site and ore quality; (2) asbestos has been shown to induce ovarian epithelial hyperplasia in guinea pigs and rabbits similar to early epithelial tumors in women[10]; (3) asbestos has been identified in talc[11]; (4) female asbestos workers have been found to have an unusually high number of peritoneal neoplasms[12]; (5) the ability of talc to migrate from the vagina to the fallopian tubes[13] and the ovaries[14-15] has been demonstrated; and (6) talc particles have been identified in both normal and neoplastic ovarian tissue[16-19].

Talc has also been implicated as a potential contributing factor in the deleterious health effects some women have reported in association with silicone breast implants. The leading cause of morbidity in women relating to silicone breast implants is capsular fibrosis[20]. In a study of tissue adjacent to silicone breast protheses a high incidence (71%) of the samples were found to contain talc particles[20]. Since talc is known to cause capsular fibrosis while silicone does not, the investigators in this study concluded that " talc may contribute to periprosthetic fibrosclerosis." Talc may be used in the manufacture of the silicone gel breast implants, perhaps as a mold release agent[20].

In a two year National Toxicology Program (NTP) study on the effects of inhaled cosmetic grade talc on rats and mice, "clear evidence of carcinogenic activity of talc in female rats" was observed.[21] The study was criticized, however, because of the small talc particle size and high concentrations used.[22] Though it has been claimed that cosmetic talc powders contain almost exclusively 200-mesh (74 μm) talc[22], there is no published data on particle size distribution of cosmetic talc.

Talc is a hydrous magnesium silicate which is widely used in a variety of cosmetic and pharmaceutical products. As a naturally occurring material, every talc deposit has a different chemical composition and morphology depending on mine location and the selection/purification processes used to isolate it[23]. The variable composition results in different grades of talc depending on the intended use of the material. According to the Cosmetic, Toiletry, and Fragrance Association, cosmetic grade talc should have a minimum of 90% hydrated magnesium silicate, with the remainder consisting of naturally associated minerals such as calcite, chlorite, dolomite, kaolin, and magnesite, and containing no detectable fibrous asbestos minerals. Asbestos is a term used to describe a group of calcium/magnesium silicates that occur in fibrous form and which have been shown to cause cancer in humans[24]. Depending on the mining site, asbestos minerals can be associated with talc deposits[25-27]. In the most recently published surveys of industrial, cosmetic and pharmaceutical talc using modern electron microscopic techniques, the presence of asbestos minerals in talc powders has been reported[26-28].

In 1983, the FDA received a citizen petition which requested that a warning statement be required on cosmetic talc products. This petition was denied in 1986 based in part on the belief that the actual levels of asbestiform minerals present in cosmetic talc had declined since the early 1970s when the problem of asbestos in talc received the attention of the agency. Another citizen petition was submitted in November, 1994, by the Cancer Prevention Coalition. The petition requests that the agency require that cosmetic talcum powder products bear a warning label such as "Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases the risk of ovarian cancer."

While the etiology of ovarian cancer is a complex issue, one area which can be conclusively addressed is a determination of whether asbestos minerals are associated with cosmetic talc products. The only published survey of cosmetic talc conducted in the U.S. using modern electron microscopic techniques was conducted twenty years ago, and the presence of asbestos was reported[26]. Data on the chemical composition, asbestos content, and particle size distribution of current market commercial talc products will be used in the evaluation of the citizen petition, and depending on the results of the survey, may be used to justify a reevaluation of the current quality assurance and GMPs of the talc industry.

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Purpose/Objectives

The purpose of the proposed study is to determine the chemical composition, the presence of fibrous materials such as asbestos, and particle size distribution of current market talc products.

Relevance to OWH and FDA missions

Health promotion and disease prevention for women is the second highest priority of FDA's Women's Health Program Initiative. Cancer is the second leading cause of death in American women with 13,300 deaths per year resulting from ovarian cancer. Epidemiological studies have shown as increased risk of ovarian cancer with talc use. The FDA is responsible for enforcing regulatory requirements for cosmetics, including that cosmetic products contain no ingredients which may render them harmful to consumers under conditions of use, and that selected ingredients are present at nontoxic levels.

Proposed Project

A survey of 50 currently marketed talc products, including baby, adult, and medicated powders (domestic and imported) will be analyzed by contract for composition, fibrous materials such as asbestos, and particle size distribution.

Methods

Approximately 50 talc products will be collected for analysis, including baby, adult, and medicated talcs. Products will be purchased in the Washington, DC metropolitan area, and will also be collected by FDA field personnel from several different areas of the U.S. By obtaining talc products from a variety of different sources, the chances of obtaining products containing talc mined from the greatest number of geographic areas will be maximized. Products will be

analyzed for mineral composition and asbestos using the methods published by Parmentier and Gill[1]. Products will be analyzed by X-ray diffraction for mineral composition followed by scanning electron microscopy for fibers. If fibrous materials are observed, the presence of asbestos will be confirmed by transmission electron microscopy. Products will also be analyzed for particle size distribution. There are several acceptable instrumentation techniques available for particle size analysis, all of which provide acceptable analytical data. The techniques employed will be determined based on the instrumentation available to the contractor.

Projected Outcomes

Data collected on current market cosmetic talc products will be used to evaluate the citizen petition currently on file with the agency. Depending on the outcome of the survey, the data may also be used to justify more stringent measures to assure talc quality.

Time Line	
March 26, 1997	Announcement of awards
May 1, 1997	Solicitation of contract
September 1, 1997	Award contract
September 1997	Purchase talc products
November 1, 1997	Progress Report
May 1, 1998	Complete final report

Budget

Fifty domestic and imported talcum powders	$700
Contract for the analysis of talc products	$45,000
Total	$45,700

[1]Parmentier, C.J. and Gill, G.J., Practical aspects of talc analysis, *National Bureau of Standards Special Publication 506* (1978).

CURRICULUM VITAE

Donald C. Havery

1. Educational Background:

1967 - 1968	Concordia Collegiate Institute, Bronxville, NY; no degree
1968 - 1969	University of Florida, Gainesville, Fl; no degree
1969 - 1969	St. Petersburg Jr. College, St. Petersburg, FL; AA degree, 1969
1970 - 1971	University of South Florida, Tampa, FL; BS degree, 1971
1975, 1977-78, 1991	George Washington University, Washington, DC; Graduate courses in Advanced Organic Chemistry I & II, Quantum Mechanics, and microbiology

2. Professional Experience:

1971 - 1972	Cooperative education student the Division of Chemistry and Physics, Food and Drug Administration, Washington, DC)
1972 - 1974	GS-5 chemist; Division of Chemistry and Physics, FDA, Washington, DC
1974 - 1975	GS-7 chemist; Division of Chemistry and Physics, FDA, Washington, DC
1975 - 1977	GS-9 chemist; Division of Chemistry and Physics, FDA, Washington, DC
1977 - 1978	GS-11 chemist; Division of Chemistry and Physics, FDA, Washington, DC
1978 - 1981	GS-12 chemist; Division of Chemistry and Physics, FDA, Washington, DC
1981 - 1990	GS-13 chemist; Division of Food Chemistry and Technology, FDA, Washington, DC)
1990 - present	GS-14 supervisory chemist; Office of Cosmetics and Colors, FDA, Washington, DC)

3. Honors and Awards

1974:	FDA quality increase
1982:	FDA commendable service award
1984:	FDA quality increase
1985:	FDA quality increase
1988:	FDA quality increase
1989:	FDA performance award
1989:	FDA quality increase
1990:	FDA performance step increase
1990:	FDA merit increase
1991:	FDA merit increase
1991:	FDA performance award
1992:	FDA Group Recognition award
1992:	FDA performance award
1993:	FDA performance award

4. Presentations:

1. "Survey of food products for volatile N-nitrosamines" (To the Association of Official Analytical Chemists, Washington, DC, October 13, 1975)
2. "Survey of finfish and shellfish for volatile N-nitrosamines" (To the Association of Analytical Chemists, Washington, DC, October 18, 1976)

3. "Trends in levels of N-nitrosopyrrolidine in fried bacon" (At the 5th meeting on the Analysis and formation of N-Nitroso Compounds, International Agency For Research on Cancer, Durham, NH, August 22, 1977)
4. "Survey of cured meat products for volatile N-nitrosamines: Comparison of two analytical methods" (At the 5th meeting on the Analysis and Formation of N-Nitroso Compounds, International Agency For Research on Cancer, Durham, NH, August 22, 1977)
5. "Human exposure to nitrosamines from foods" (At the annual meeting of the Institute of Food Chemists, Anaheim, CA, June 10, 1984)
6. "Survey of baby bottle rubber nipples for volatile N-nitrosamines" (To the Association of Analytical Chemists, Washington, DC, October 25, 1982)
7. "Nonvolatile N-nitrosamine investigations: Method for the determination of N-nitrosoamino acids and preliminary results of the development of a method for the determination of N-nitrosodipeptides N-terminal in proline" (At the 8th meeting on N-Nitroso Compounds; Occurrence and Biological Effects International Agency For Research on Cancer, Banff, Canada, September 4, 1983)
8. "A post/column reaction system for the detection of N-nitroso compounds by HPLC with a thermal energy analyzer" (At a conference entitled: The Advances in the Biology and Chemistry of N-nitroso and Related Compounds, Eppley Institute, Omaha, NB, May 19, 1988)
9. "A post/column reaction system for the detection of N-nitroso compounds by HPLC with a thermal energy analyzer" (At a National Institutes of Health seminar, Gaithesburg, MD, December 2, 1988)
10. "The use of chemiluminescence" (At a seminar entitled "Advanced Chromatographic Techniques", Food and Drug Administration, Detroit, MI, July 10, 1990)
11. "Nitrosamines in sunscreens and cosmetic products: occurrence, formation and trends" (ACS National Meeting, Washington, DC, August 23-28, 1992)
12. "N-Nitroso compounds: occurrence, and determination" (Society of Cosmetic Chemists Meeting, New York, New York, December 3-4, 1992)
13. "Overview of the occurrence and determination of N-nitroso compounds in food and cosmetics" (Cosmetic, Toiletry and Fragrance Association, Meeting of the Scientific Advisory Committee, Alexandria, Virginia, January 15, 1993)
14. "Nitrosamines in Cosmetics" (FDA Office of Cosmetics and Colors seminar; June 30 and October 4, 1994).
15. "Analysis of cosmetic raw materials and products" (American Chemical Society Middle Atlantic Meeting; Washington, DC; May 25, 1995)

5. Publications:
Forty publications and book chapters on analytical methods for the determination of compounds of toxicological interest to the agency such as N-nitroso compounds, ethyl carbamate and fragrance ingredients.

6. Offices Held in Professional Societies:
1995 to present Member of the Committee on Scientific Affairs; Society of Cosmetic Chemists

February 4, 1994

Chief, Cosmetics Technology Branch (HFS-127)

Summary of Talc Symposium: Consumer Uses and Health Perspectives

Adele Dennis
Director, Division of Science and Applied Technology
(HFS-125)

Talc Inhalation Studies

Talc: hydrous magnesium silicate; 900,000 tons/year used in the US; 48,000 tons/yr (6%) in cosmetics. Treatment of raw talc for cosmetic use results in 90-95% pure talc. Uses: powders, antiperspirants, pill coatings/fillers, foods (chewing gum/anticaking), medical devices (surgical glove/condom coating; Note: no longer used in surgical gloves). Cosmetic uses: antiperspirants, semi-solid matrices (eye shadow), powders. Talc used in powders is 200 mesh and is the only cosmetically used talc which has the potential for being inhaled. This particle size is too large to be respirable however. Most talc particles in powders will be trapped in the nose. Talc and asbestos materials are not formed under the same geologic conditions, therefore careful selection of mining sites results is asbestos-free talc. Estimated human exposure via respiration when using powder during baby diapering: 0.2 - 2 mg/m^3.

NTP study: Requested by NIOSH due to worker exposure. Talc particles smaller than typically used in cosmetic products were used in the NTP study to determine the effects on inhalation. Larger particles would not have made it into the lungs. Two year study; exposure levels tested in chronic study: 6, 18 mg/m^3. Rodent exposure 2,000 - 20,000 times greater than estimated human exposure. Tumors formed only in female rats at the highest dose. The species of female rats used are known to be particularly sensitive to particulates. No tumors were observed in male or female mice. Adrenal medulla neoplasms were also observed in rats; origin is unknown. Talc exposure tested at the highest level was an "overload"; clearance time from the lung at this concentration is greatly increased. The smaller the particles the longer the clearance time. In a related study, there was no evidence for increased incidence of lung tumors in coal mine workers exposed to coal dust whose estimated exposure was greater than the exposure to particles in the talc rat study. TiO_2, chromium dioxide, volcanic ash and quartz dust have all produced tumors in female rats (not male rats), by inhalation. A negative dust control was not included in the NTP study which raises the question: did the observed tumors result from talc or would they have arisen from any particulate? There was one member of the NTP review panel who did not agree with the conclusions prepared by the study team. This person's comments included: (1) the maximum tolerated dose was exceeded at 18 mg/m^3, and was therefore inappropriate; (2)

there was an increase in tumors in the controls over that observed historically for this animal which was neglected in the study conclusions. Historically, talc has been used as the negative control for inhalation studies on silica and asbestos.

Caution was urged when extrapolating the rodent study results to man. Lung branching between rodents and man is different and this will effect which cells are exposed to particulates.

Ovarian Cancer and Talc Use

US annual incidence of ovarian cancer: 15 per 100,000; 8 per 100,000 deaths per year. Trends in mortality and incidence of ovarian cancer have been stable for 20 years. Factors which decrease incidence: use of oral contraceptives, breast feeding, child bearing, hysterectomy. (ie. Activities which reduce the number of times the ovary has to repair itself following release of an egg).

Talc can migrate to the ovaries, though the route is presently unknown. There is some evidence that particulates can migrate to other body tissues via the vascular system. Intestinal absorption is negligible. Radiolabeled talc injected vaginally into rabbits did not migrate to the ovaries.

Questions about talc migration to ovaries originated with a study published by Henderson in 1971 in which talc was found in human ovaries. The study was repeated in 1979 and talc was again found, this time in the ovaries of nontumoragenic women. These studies may have been flawed. Controls may not have been adequately conducted. In another experiment, labeled talc was deposited in the vagina but no translocation to the ovaries was detected. Analytical techniques used by Henderson to determine talc were questioned. Since many minerals are structurally similar, misidentification was likely. Only in the last ten years have methods become available for reliable talc measurement. Mineralogical methods were used to measure talc particulates and not histological techniques. Ovary tissues may have been removed by physicians using gloves contaminated with talc (though in the second study, ovarian tissue was removed with forceps only). Talc granulomas following surgery due to talc on gloves has been reported, but no granulomas were reported in Henderson's studies, raising questions about what particulates Henderson actually observed.

There have been 9 epidemiological studies of the relationship between talc use and ovarian cancer. Two studies showed a statistically significant increase in cancer incidence, the other studies showed a negative correlation. The risk of ovarian cancer prior to 1960 was greater than after 1960. This could be due to the reduction of asbestos fibers in talc due to modern processing techniques. Epidemiological studies suggest a small risk of ovarian cancer for talc

users: 1.3 relative risk where 1.0 is equivalent to no risk. There are a number of confounders which will influence epidemiological studies including race, marital status, age, education, history of tubal ligation, use of oral contraceptives, and asbestos exposure. Inherent bias of epidemiological studies were also mentioned including inaccurate interview information (eg. recollection).

A six fold increase in ovarian cancer has been identified between women in the U.S. and Japan. This may be attributed to dietary fat intake.

General Conclusion: Additional information is needed to make a definitive conclusion about talc use and ovarian cancer. Presently the increased risk of ovarian cancer due to talc exposure is a hypothesis which remains to be tested.

Donald C. Havery

Talc: *(Purpose: As a follow-up to the 1994 talc symposium, to identify the chemical composition of talc, and to evaluate the identity of the material used in the NTP study on the carcinogenicity of talc particles in mice)* F. Hurley continued writing up a review of CTFA's comments to the citizen's petition relating to talc. A copy of the petition itself was obtained for review.

N-Nitrosamines: D. Havery, R. Yates, and H. Chou continued worked on a malfunctioning Thermal Energy Analyzer instrument used for N-nitrosamine analysis. It was determined that the photomultiplier tube had cracked and was bad. Fortunately we have a spare, since a new tube costs $2,000.

Other: R. Yates drafted an annual report on the activities of this project in FY95.

D. Havery drafted a letter to a scientist in The Netherlands in response to a request for a sample of 2-ethylhexyl 4-(N-nitroso-N-methylamino) benzoate. The letter was finalized. and the sample was mailed.

G. Black continued working on the inventory of CTEB's chemicals and cosmetic raw materials.

Manuscript Status: (Status changes indicated in bold type)

Accepted by the Journal:

"Determination of 2-Ethylhexyl 4-(N-methyl-N-nitrosamino) Benzoate in Commercial Sunscreens and Cosmetic Products" (Galley reviewed; publication scheduled for the November/December issue)

Under review by Technical Editing:

"Nitro musks in fragrance products - An update of FDA findings"

Under Review at the Branch level:

"A Rapid Method for the Determination of Nitrosating Agents in Cosmetic Products by Chemiluminescence Detection of Nitric Oxide"

"Determination of Formaldehyde Donating and Paraben Preservatives in Cosmetic Products by Solid Phase Extraction"

"Surveys of Commercial Fragrance Products from 1985-1992 for Nitro Musks"

"Determination of musk ambrette, musk xylol, and musk ketone in fragrance products by capillary gas chromatography with electron capture detection"

"Determination of 1,4-dioxane in ethoxylated cosmetic raw materials and in cosmetic finished products"

"Determination of contaminants in fatty acid diethanolamides"

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June 30,1994

Dr.John Bailey, Director
Office of Cosmetics and Colors
Food and Drug Administration
200 C Street, S.W.
Washington, D.C. 20204

Dear John:

As agreed, I am enclosing a confidential prepublication manuscript of my review article titled "Biological Effects of Cosmetic Talc". The manuscript has been accepted for publication in FOOD AND CHEMICAL TOXICOLOGY. Please do not quote or refer to it until it has been published.

As discussed, I am also enclosing for your ready reference several reprints on animal studies in which I was personally involved as project director and toxicologist. The talc inhalation studies in hamsters show that no talc-induced lesions -- not even fibrosis -- developed in the exposed animals at the selected talc aerosol concentrations which -- although 30 to 1700 times those of median infant exposures -- were below those causing lung overload conditions. The Lovelace study was criticized at the January 31/February 1 FDA workshop because even the low-dose exposure (6 mg/m^3) resulted in a lung overload.

As to translocation of highly insoluble particles from the vagina to the ovaries without inadvertent or deliberate assistance, several studies, including our own, were unable to show any such migration. The results of several others, seemingly indicating translocation, can be plausibly explained in most cases by other phenomena, such as false positives (Egli and Newton,1961); Trendelenberg position of patients and multipara with lacerated cervix (DeBoer,1972); radionuclide leached from the particles rather than translocated particles (Venter and Iturralde,1979); etc. Yet, talc particles have been reported in human ovaries (e.g.,Henderson et al, 1971, 1978, 1979). To the best my knowledge it remains unexplained how highly insoluble

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inanimate particles without locomotion of their own and unable to respond to chemotactic stimuli can breach the formidable cervical barrier and "swim upstream" against menstrual flow and the beat of the cilia in the oviducts to reach the ovaries, seemingly defying the laws of physics. It is noteworthy that none of the investigators having reported an association between hygienic talc use and ovarian cancer is claiming a causal relationship.

Please contact me if you have any questions.

Sincerely

Al

Dr.Alfred P.Wehner

C T F A

THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

E. EDWARD KAVANAUGH
PRESIDENT

September 9, 1994

Donald C. Havery
Office of Cosmetics and Colors
Food and Drug Administration
200 C Street, S.W.
Washington, DC 20204

Dear Mr. Havery,

Thank you for your letter of inquiry dated June 7, 1994. I have responded previously (June 8, 1994) by forwarding you a copy of the manuscript entitled *Talc: Occurrence, Characterization and Consumer Applications (Zazenski et al., 1994)*. We have since made some minor revisions to the manuscript (enclosed).

The answers to the specific questions in your letter are as follows:

> ***[It was] mentioned at the [ISRTP] Talc Symposium that cosmetics grade talc is 200 mesh, and that it goes through a process to give 90-95% pure talc. In the CTFA Compendium Specifications, talc is defined as "..... containing no detectable fibrous, asbestos minerals". Is this the specification for cosmetic grade talc presently used in the industry?***
>
> *Answer: Yes.*
>
> ***Does the cosmetic industry run QC tests for asbestos in the talc they use?***
>
> *Answer: Yes, both suppliers and manufacturers of finished talc-containing products run QC tests to confirm the absence of asbestos.*
>
> ***Do talc producers certify batches of talc for composition and fiber content? If so how long have they been doing this? Do they use x-ray diffraction as suggested by the CTFA?***

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202.331.1770 FAX 202.331.1969
SECURING THE INDUSTRY'S FUTURE SINCE 1894

[redacted]

Johnson & Johnson
CONSUMER PRODUCTS COMPANY

(b) (5) [redacted]

VIA FEDERAL EXPRESS

February 26, 1999

John Bailey, PhD.
Director, Division of Colors and Cosmetics
CFSAN
Food and Drug Administration
200 "C" Street
Washington, DC 20204

Dear Dr. Bailey:

Enclosed please find a copy of Talc: An Overview published in *Comments on Technology, Vol.6 Number 5, 1998.*

I am sending this to you because it is not on the Lexis/Nexus database.

We are very concerned about the proposed amendment of State of New York Senate Bill 1462, that mandates a safety warning on cosmetic talc products (copy attached).

We hope that this recent overview of talc safety will be of assistance to you in preparing the Agency position on this bill.

Please call me at (908) 874-1337 if you have any questions.

Yours truly,

Marjorie B. McTernan
Director Regulatory Affairs

SB1462

S1462 HEVESI

STATE OF NEW YORK

1462

1999-2000 Regular Sessions

IN SENATE

January 22, 1999

Introduced by Sen. HEVESI -- read twice and ordered printed, and when printed to be committed to the Committee on Consumer Protection

AN ACT to amend the general business law, in relation to labeling of cosmetic talc products

The People of the State of New York, represented in Senate and Assembly, do enact as follows:

Section 1. The general business law is amended by adding a new section 399-y to read as follows:

§ 399-y. Labeling of cosmetic talc products. 1. No person, firm or corporation shall sell or offer for sale any cosmetic talc product unless there is printed on the package in which such talc product is sold or offered for sale a warning label, prominently displayed, which states, "Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases the risk of ovarian cancer."

2. Any violation of this section shall be punishable by a civil penalty not to exceed one thousand dollars.

§ 2. This act shall take effect 120 days after it shall have become a law.

EXPLANATION--Matter in *italics* (underscored) is new; matter in brackets [-] is old law to be omitted.

LBD06700-01-9

PRESCRIBING INFORMATION **NDC 63256-200-04**

STERILE TALC POWDER

FDA FINAL VERSION

For Intrapleural Administration Only

DESCRIPTION

Sterile Talc Powder is a sclerosing agent intended for intrapleural administration supplied in a single use 100 mL brown glass bottle, sealed with a gray, 20 mm stopper and covered with a flip-off seal. Each bottle contains a minimum of 5.0 g of Talc *USP* (Ultra 2000 Talc), either white or off-white to light gray, asbestos-free and brucite-free grade of talc of controlled particle size. The composition of the talc is ≥ 95% talc as hydrated magnesium silicate. The empirical formula of talc is (b) (4) with a molecular weight of (b) (4) Associated naturally occurring minerals include (b) (4) (b) (4) , (b) (4) (b) (4) (b) (4) , (b) (4) (b) (4) and (b) (4) Talc is practically insoluble in water and in dilute solutions of acids and alkali hydroxides. The finished product has been sterilized by gamma irradiation.

CLINICAL PHARMACOLOGY

Mechanism of Action

The therapeutic action of talc instilled into the pleural cavity is believed to result from induction of an inflammatory reaction. This reaction promotes adherence of the visceral and parietal pleura, obliterating the pleural space and preventing reaccumulation of pleural fluid.

The extent of systemic absorption of talc after intrapleural administration has not been adequately studied. Systemic exposure could be affected by the integrity of the pleural surface, and therefore could be increased if talc is administered immediately following lung resection or biopsy.

CLINICAL STUDIES

The data demonstrating safety and efficacy of talc slurry administered via chest tube for the treatment of patients with malignant pleural effusions are from the published medical literature. The following prospective, randomized studies were designed to evaluate the risk of recurrence of malignant pleural effusions in patient with a variety of solid tumors. The studies compared talc slurry, instilled into the pleural cavity via chest tube, versus a concurrent control. In all studies, after maximal drainage of the pleural effusion, the investigator administered talc slurry via the chest tube. Chest films documented response (defined as lack of recurrence of fluid for a period of time). Studies differed on the timing of the efficacy assessment. Zimmer *et al*. did not

specify the time required evaluations. Ong *et al.* specified the assessment at one month. Sorensen *et al.* specified the assessment at 3-4 months. The remaining studies assessed response at the completion of the follow-up period.

Randomized Controlled Trials Using Talc Slurry as a Sclerosing Agent

REFERENCE	TREATMENT	RESPONSE RATE EVALUABLE PTS* p value*	RESPONSE RATE ALL PTS* p value*
Sorensen *et al.* Eur J Respir Dis. 1984: 65(2):131-5	Talc Slurry 10g /250ml NS vs. Chest tube drainage alone	100% (9/9) vs. 58% (7/12) p=0.04	64% (9/14) vs. 41% (7/17) p=0.29
Noppen *et al*. Acta Clin Belg 1997; 52(4):258-62	Talc Slurry 5g/50-ml NS vs. Bleomycin 1mg/kg/50ml NS	79% (11/14) vs. 75% (9/12) p=1.00	79% (11/14) vs. 75% (9/12) p=1.00
Zimmer PW *et al.* Chest 1997; 112(2):430-434	Talc Slurry 5g/50 ml NS[c] vs. Bleomycin 60U/50 ml NS[c]	90% (17/19[b]) vs. 79% (11/14 [b]) p=0.63	Not Given
Ong KC *et al.* Respirology 2000;5;99-103	Talc Slurry 5g/150ml NS[d] vs. Bleomycin 1U/kg/150 ml NS[d]	89% (16/18) vs. 70% (14/20) p=0.24	64% (16/25) vs. 56% (14/25) p=0.77
Yim AP *et al.* Ann Thorax Surg 1996; 62:1655-8	Talc Slurry 5g/50ml NS, lidocaine 2% 10 ml vs. Talc Insufflation 5g powder	90%(26/29) vs. 96% (27/28) p=0.61	90% (26/29) vs. 96% (27/28) p=0.61

* Two-sided p-value based on Fisher's exact test

[a] Patients were evaluable if chest x-rays were done to assess response per protocol.
The Sorensen study excluded patients if incomplete lung re-expansion was noted post drainage.

[b] Data per procedure (33 procedures in 29 evaluable patients, 3 patients with bilateral effusions).

[c] Plus lidocaine 1%, 20 ml.

[d] Plus lidocaine 1%, 10 ml.

In single-arm studies of malignant pleural effusions from the published literature, variously defined "success" rates using talc slurry pleurodesis ranged from 75% to 100%.

INDICATIONS AND USAGE

Sterile Talc Powder, administered intrapleurally via chest tube, is indicated as a sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients.

CONTRAINDICATIONS

None known

WARNINGS

None

PRECAUTIONS

1. **Future procedures:** The possibility of the future diagnostic and therapeutic procedures involving the hemithorax to be treated must be considered prior to administering Sterile Talc Powder. Sclerosis of the pleural space may preclude subsequent diagnostic procedures of the pleura on the treated side. Talc sclerosis may complicate or preclude future ipsilateral lung resective surgery, including pneumonectomy for transplantation purposes.

2. **Use in potentially curable disease:** Talc has no known antineoplastic activity and should not be used alone for potentially curable malignancies where systemic therapy would be more appropriate, e.g., a malignant effusion secondary to a potentially curable lymphoma.

3. **Pulmonary complications:** Acute Pneumonitis and Acute Respiratory Distress Syndrome (ARDS) have been reported in association with intrapleural talc administration. Three of the case reports of ARDS have occurred after treatment with a relatively large talc dose (10 g) administered via intrapleural chest tube instillation. One patient died one month post treatment and two patients recovered without further sequelae.

DRUG INTERACTIONS

It is not known whether the effectiveness of a second sclerosing agent after prior talc pleurodesis would be diminished by the absorptive properties of talc.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies on the carcinogenicity of talc have been performed using non-standard designs which prevent firm conclusions on its carcinogenicity. With single intraperitoneal administration to mice at 20 mg and observation for at least 6 months or 4 weekly doses administered intraperitoneally at 25 mg/dose to rats with observation for at least 84 weeks, tumor incidence was not increased. In these studies the talc

and its asbestos content were not characterized.

Genotoxicity was tested in cultures of rat pleural mesothelial cells (RPMC) as unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs). None of the talc samples (which were asbestos-free) induced enhancement of UDS or SCEs in treated cultures. No information is available on impairment of fertility in animals by talc.

Pregnancy: Pregnancy Category B. An oral administration study has been performed in the rabbit at 900 mg/kg. Approximately 5 fold higher than a human dose on mg/m^2 basis, and has revealed no evidence of teratogenicity due to talc. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless the benefit outweighs the risk.

Pediatric Use: The safety and efficacy of Sterile Talc Powder in pediatric patients have not been established.

Geriatric use: The estimated mean and median ages of patients treated with talc slurry from clinical studies (single-arm or randomized) were 60 and 62 years, respectively. No analyses to specifically evaluate the safety and efficacy in the geriatric population have been reported.

ADVERSE REACTIONS

Intrathoracic administration of talc slurry has been described in medical literature reports involving more than 2000 patients. Patients with malignant pleural effusions were treated with talc via poudrage or slurry. In general, with respect to reported adverse experiences, it is difficult to distinguish the effects of talc from the effects of the procedure(s) associated with its administration. The most often reported adverse experiences to intrapleurally-administered talc were fever and pain.

Infection: Complications reported include empyema.

Respiratory: Complications reported include hypoxemia, dyspnea, unilateral pulmonary edema, pneumonia, ARDS, brochopleural fistula, hemoptysis and pulmonary emboli.

Cardiovascular: Complications reported included tachycardia, myocardial infarction**,** hypotension, hypovolemia, and asystolic arrest

Delivery Procedure: Adverse reactions due to the delivery procedure and the chest tube may include: pain, infection at the site of thoracostomy or thoracoscopy, localized bleeding, and subcutaneous emphysema.

Chronic Toxicity: Since patients in clinical studies had a limited life expectancy, data on chronic toxicity are limited

OVERDOSAGE

No definite relationship between dose and toxicity has been established. Excessive talc may be partially removed with saline lavage.

DOSAGE AND ADMINISTRATION

Sterile Talc Powder should be administered after adequate drainage of the effusion. The success of the pleurodesis appears to be related to the completeness of the drainage of the pleural fluid, as well as the full re-expansion of the lung, both of which will promote symphysis of the pleural surfaces.

The recommended dose is 5 g, dissolved in 50 - 100 ml Sodium Chloride Injection, *USP*. Although the optimal dose for effective pleurodesis is unknown, 5 g was the dose most frequently reported in the published literature.

Talc Preparation

Prepare the talc slurry using aseptic technique in an appropriate laminar flow hood. Remove talc container from packaging. Remove protective flip-off seal.

Each brown bottle contains 5 g of Sterilized Talc Powder. To dispense the contents:

1. Using a 16 gauge needle attached to a 60-ml LuerLok syringe, measure and draw up 50 ml of Sodium Chloride Injection, *USP*. Vent the talc bottle using a needle. Slowing inject the 50 ml of Sodium Chloride Injection, *USP* into the bottle. For doses more than 5 g, repeat this procedure with a second bottle.

2. Swirl the bottle(s) to disperse the talc powder and continue swirling to avoid settling of the talc in the slurry. Each bottle will contain 5 g Sterile Talc Powder dispersed in 50 ml of Sodium Chloride Injection, *USP*.

3. Divide the content of each bottle into two 60 ml irrigation syringes by withdrawing 25 ml of the slurry into each syringe with continuous swirling. QS each syringe with Sodium Chloride Injection, *USP* to a total volume of 50 ml in each syringe. Draw air into each syringe to the 60 ml mark to serve as a headspace for mixing prior to administration.

4. When appropriately labeled, each syringe contains 2.5 g of Sterile Talc in 50 ml of Sodium Chloride Injection, *USP* with an air headspace of 10 ml. Once the slurry has been made, use within 12 hours or discard and prepare fresh slurry. Label the syringes appropriately noting the expiration date and time, with the statement “For Pleurodesis Only – NOT FOR IV ADMINISTRATION,” the identity of the patient intended to receive this material and a

cautionary statement to SHAKE WELL before use.

5. Prior to administration, completely and continuously agitate the syringes to evenly redisperse the talc and avoid settlement. Immediately prior to administration, vent the 10 ml air headspace from each syringe.

6. Attach the adapter and place a syringe tip on the adapter. Maintain continuous agitation of the syringes.

NOTICE: Shake well before installation. Each 25 ml of prepared slurry in the syringe contains 1.25 g of talc. NOT FOR IV ADMINISTRATION.

Administration

Administer the talc slurry through the chest tube by gently applying pressure to syringe plunger and empty the contents of the syringe into the chest cavity. After application, discard the empty syringe according to general hospital procedures. After the talc slurry has been administered through the chest tube into the pleural cavity, the chest tube may be flushed with 10- 25 ml sodium chloride solution to ensure that the complete dose of talc is delivered.

Following introduction of the talc slurry, the chest drainage tube is clamped, and the patient is asked to move, at 20 to 30 minute intervals, from supine to alternating decubitus positions, so that over a period of about 2 hours the talc is distributed within the chest cavity. Recent evidence suggests that this step may not be necessary.

At the end of this period, the chest drainage tube is unclamped, and the excess saline is removed by the routine continual external suction on the tube.

HOW SUPPLIED

NDC 63256-200-04 Sterile Talc Powder is supplied in a 100 ml brown glass bottle containing 5 g of talc. The sterile bottle is closed with a gray stopper and covered with a flip-off seal.

Storage: Store at Room Temperature (18-25°C). Protect against sunlight.

DISTRIBUTED BY: (b) (4) [redacted]

Version: Original September 2003

Lipnicki, John

From: Katz, Linda
Sent: Friday, May 07, 2004 12:35 PM
To: Stone, Theresa H
Cc: Castro, Veronica; Katz, Linda
Subject: FW: Cosmetics Questions

See responses below. If you need any additional information, please let me know.

Why is talc, a known carcinogen, still allowed in cosmetics?

FDA does not have premarket approval authority for cosmetic products or ingredients (with the exception of color additives). Thus, it is the responsibility of the manufacturer to assess cosmetic products before marketing to assure that they fully comply with all applicable laws and regulations that we enforce, regarding safety. If the safety of the product (or any of the ingredients) has not been substantiated prior to marketing, then the following statement must appear conspicuously on the principal display panel for the product: "Warning--The safety of this product has not been determined." (See 21 CFR 740.10(a)).

According to the National Toxicology Program (NTP), its initial review of talc for possible listing in the 10th Edition of the Report on Carcinogens (RoC) found that there is some confusion in the scientific literature over the mineral nature and consequences of exposure to talc, both containing asbestiform fibers and not containing asbestiform fibers. The NTP decided to defer consideration of listing talc in the 10th RoC and a careful review of the literature on these materials is underway to determine if a clear definition of the agent or agents involved in human exposures can be developed. [http://ntp-server.niehs.nih.gov/NewHomeRoc/Talcstatus.html]

How does the FDA decide what can be considered a trade secret? (This answer is applicable only to cosmetics.)

FDA grants this status under very limited circumstances and after careful review of the manufacturer's data. The manufacturer must prove that the ingredient imparts some unique property to a product and that the ingredient is not well-known in the industry. FDA considers, among other things, scientific or technical data, reports, tests, and other relevant information that address several specific factors (see 21 CFR 720.8) about whether the identity of an ingredient qualifies as a trade secret. Requests for confidentiality of cosmetic ingredients are handled in accordance with the procedures in 21 CFR 720.8 and 21 CFR 20.44.

What chemicals are considered trade secrets? Is there any way consumers can find out what these ingredients are?

A determination of confidentiality of a trade secret by FDA, in accordance with 21 CFR 20.44, means that such data or information will not be made available for public disclosure unless the agency is ordered to do so by a court.

Why aren't all fragrance ingredients listed?

In response to comments submitted before publication of the final

regulation on ingredient labeling on October 17, 1973 (38 FR 28912), the agency concluded that listing all ingredients of fragrances (which might contain 20 or more ingredients) would be impractical and could distract from the listing of other, more significant ingredients.

As of April 19, 2001, the FDA said it was evaluating study data from a CDC report on phthalates to determine whether the levels described by the CDC report are a health concern. Has the agency finished studying that data? If so, what is the conclusion?

FDA reviewed the safety/toxicity data (including the CDC data) for phthalates in 2001 and 2002 as the Cosmetic Ingredient Review (CIR) Expert Panel was conducting its review of the safety of dibutylphthalate. (The CIR is an industry-sponsored organization that reviews cosmetic ingredient safety and publishes its results in open, peer-reviewed literature.) In November 2002, the CIR reaffirmed its original conclusion that dibutyl phthalate is safe as used in cosmetic ingredients. The panel concluded that exposures to phthalates from cosmetics are low compared to levels that would cause adverse effects in animals. Therefore, there is a high margin of safety between exposure to cosmetics and doses that cause observable toxicity in animal tests. This conclusion appears reasonable in light of the currently available data and FDA does not believe that users of cosmetic products containing phthalates are at risk for adverse effects. However, FDA continues to monitor the situation in case new data appears that suggests a significant level of risk.

The CDC report only noted levels of phthalates excreted in urine. It did not establish any association between phthalates and health risks to humans, nor the source of the exposure, nor any association between the use of cosmetics and health risks.

Is the FDA planning for follow the EU in banning phthalates from nail polishes?

As stated above, under the law, cosmetic products and ingredient are not subject to premarket approval. A cosmetic (other than coal-tar hair dyes, which the law treats differently) would be considered adulterated, and subject to action by FDA, if it contained a substance that is "poisonous or deleterious." However, at this time, FDA does not have evidence that phthalates, as used in cosmetics, pose a safety risk.

Are there any chemicals that the FDA has banned from cosmetics?

The use of the following ingredients in cosmetics is prohibited or restricted by regulation (21 CFR part 700): hexachlorophene, mercury compounds, chlorofluorocarbons, bithionol, halogenated salicylanilides, chloroform, vinyl chloride, zirconium-containing complexes, and methylene chloride. FDA promulgated these regulations through the notice and comment public rulemaking process when it had convincing evidence regarding health concerns associated with these ingredients.

Linda M. Katz, M.D., M.P.H.
Director, Office of Cosmetics and Colors
Food and Drug Administration
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway, HFS-100
College Park, Maryland 20740
202- 418-3412

-----Original Message-----
From: Castro, Veronica

Bailey, Catherine J

From: Meyers, Beth
Sent: Thursday, July 29, 2004 2:36 PM
To: Bailey, Catherine J
Subject: FW: Cosmetics Questions/Phthalates

Kitty,

The message below (see section in blue) may be ~~the phthalates~~ one of the phthalates communications that have come up since the fact sheet and talking points were developed. I'll see what I can do with the most recent inquiry.

Beth

-----Original Message-----
From: Lipnicki, John
Sent: Friday, May 07, 2004 10:20 AM
To: Meyers, Beth
Subject: FW: Cosmetics Questions

Beth,

(b) (5) [redacted]. Please forward the complete draft to Linda when final with a cc to me. Thanks again.

John

Why is talc, a known carcinogen, still allowed in cosmetics?

Generally speaking, since FDA does not have premarket approval authority for cosmetic products or their labels, it remains the responsibility of the manufacturer to assure that each ingredient used in a cosmetic product and each finished cosmetic product be adequately substantiated for safety prior to marketing so that they fully comply with all applicable laws and regulations that we enforce (e.g., cosmetics are safe and properly labeled). If the safety of the product (or any of the ingredients) has not been substantiated prior to marketing, then the following statement must appear conspicuously on the principal display panel for the product: "Warning--The safety of this product has not been determined." (See 21 CFR 740.10(a)).

According to the National Toxicology Program (NTP), its initial review of talc for possible listing in the 10th Edition of the Report on

Carcinogens (RoC) found that there is some confusion in the scientific literature over the mineral nature and consequences of exposure to talc, both containing asbestiform fibers and not containing asbestiform fibers. The NTP decided to defer consideration of listing talc in the 10th RoC and a careful review of the literature on these materials is underway to determine if a clear definition of the agent or agents involved in human exposures can be developed. [http://ntp-server.niehs.nih.gov/NewHomeRoc/Talcstatus.html]

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-----Original Message-----
From: Katz, Linda
Sent: Thursday, May 06, 2004 1:16 PM
To: Lipnicki, John; Meyers, Beth
Subject: FW: Cosmetics Questions

Beth & John –

See questions below. (b) (5) [redacted]

Linda

-----Original Message-----
From: Castro, Veronica
Sent: Thursday, May 06, 2004 11:40 AM
To: Katz, Linda
Cc: Stone, Theresa H
Subject: RE: Cosmetics Questions

Linda,

Please see below. Do you have time to prep Diana (PAS in NY-DO) before her interview next week? If not, can someone in OCC do it?

Thanks
Veronica

-----Original Message-----
From: Stone, Theresa H
Sent: Thursday, May 06, 2004 11:36 AM
To: Castro, Veronica
Subject: RE: Cosmetics Questions

I do think that if Diana does the interview, you'll need some backgrounding on some of the issues the reporter is interested in. (b) (5) [redacted]

-----Original Message-----
From: Castro, Veronica
Sent: Thursday, May 06, 2004 11:33 AM
To: Stone, Theresa H

Subject: RE: Cosmetics Questions

Oh, OK. The reporter contacted me this morning and asked for status. I told her that I'd forwarded the request to you and should have an answer for her today. Let me know if you need anything else from me.

-----Original Message-----
From: Stone, Theresa H
Sent: Thursday, May 06, 2004 11:31 AM
To: Castro, Veronica; Monaco, Diana D
Subject: RE: Cosmetics Questions

Veronica, my question was addressed to Diana, not you. I think it would be better if she contacted the reporter herself to set up a time next week.

-----Original Message-----
From: Castro, Veronica
Sent: Thursday, May 06, 2004 11:07 AM
To: Stone, Theresa H
Subject: RE: Cosmetics Questions

I will do that. Will they come to Diana's office? If so, I need her address.

-----Original Message-----
From: Stone, Theresa H
Sent: Thursday, May 06, 2004 10:44 AM
To: Monaco, Diana D
Cc: Castro, Veronica
Subject: RE: Cosmetics Questions

Is it possible for you to just call the reporter today, and set up a time for early next week?

-----Original Message-----
From: Monaco, Diana D
Sent: Thursday, May 06, 2004 8:45 AM
To: Stone, Theresa H
Subject: RE: Cosmetics Questions

I just rec'd this - (Thursday AM) - I was out yesterday and out tomorrow and booked today - which means if it is really for this week I cannot - but I am happy to do it next week.(Mon Tues or Thurs)

Let me know - Diana

"The contents of this message are mine personally and don't reflect any position of the Government or FDA."
Diana D. Monaco, RD, CDN
Public Affairs Specialist
FDA - NY District
Olympic Towers, Suite 100
300 Pearl Street
Buffalo, NY 14202
716-541-0318
FAX:716-551-3845

-----Original Message-----
From: Stone, Theresa H
Sent: Wednesday, May 05, 2004 8:59 AM
To: Monaco, Diana D
Cc: Castro, Veronica

Subject: FW: Cosmetics Questions

(b) (5) [redacted] Just let me know.

-----Original Message-----
From: Castro, Veronica
Sent: Wednesday, May 05, 2004 8:21 AM
To: Stone, Theresa H
Cc: Katz, Linda
Subject: FW: Cosmetics Questions

Theresa,

Please see below.
-----Original Message-----
From: Tara Moncheck [mailto:tara.moncheck@wten.com]
Sent: Tuesday, May 04, 2004 4:38 PM
To: vcastro@oc.fda.gov
Subject: Cosmetics Questions

Dear Veronica,

As per our phone conversation yesterday, here are some questions I'd like to discuss during an interview. Please let me know if someone from the FDA is available in the Albany, NY area this week. If so, we would like to set up an on-camera interview.

Why is talc, a known carcinogen, still allowed in cosmetics?

How does the FDA decide what can be considered a trade secret?

What chemicals are considered trade secrets?

Is there any way consumers can find out what these ingredients are?

As of April 19, 2001, the FDA said it was evaluating study data from a CDC report on phthalates to determine whether the levels described by the CDC report are a health concern. Has the agency finished studying that data? If so, what is the conclusion?

Is the FDA planning for follow the EU in banning phthalates from nail polishes?

Why aren't all fragrance ingredients listed?

Are there any chemicals that the FDA has banned from cosmetics?

Thanks for your help!

Sincerely,
Tara Moncheck
NEWS10 Investigates Producer
518-433-4229
518-433-4291 - Fax

MessageFrom: Bailey, Catherine J
Sent: Monday, August 15, 2005 6:38 AM
To: Meyers, Beth
Cc: Lipnicki, John
Subject: FW: Talcum powder

For the files.
Thanks.

-----Original Message-----
From: Milstein, Stanley R
Sent: Friday, August 12, 2005 6:20 PM
To: 'Jennifer Butler'
Cc: Lipnicki, John; Bailey, Catherine J; Katz, Linda; Holman, Matthew Ray; 'Luisa_Carter-Phillips@hc-sc.gc.ca'
Subject: RE: Talcum powder

Hi, Jennifer!

I have looked for information that would be responsive to your inquiry. Here is what I have been able to find:

General:

FDA regulates cosmetics and color additives under the 1938 Federal Food, Drug, and Cosmetic Act (FFDCA), as well as the 1960 Color Additive Amendments to the Act and the 1966 Fair Packaging and Labeling Act (FPLA). Our mandate for cosmetics and their ingredients, however, does not include pre-market approval nor pre-market notification authority; all color additives used in FDA-regulated products, however, are subject to pre-market approval.

Talc: Cosmetic Ingredient, Drug Ingredient, and Color Additive

Talc is a bonafide cosmetic ingredient; it is monographed in the CTFA International Cosmetic Ingredient Dictionary (ICID) and also appears in the U.S. Pharmacoepia (USP), where specifications are given; the Cosmetic Ingredient Review (CIR) has not conducted a safety assessment for cosmetic talc, to date . According to the FDA 2004 Voluntary Cosmetic Registration Program (21 CFR 720) “Frequency of Use (FoU)” Database, the number of cosmetic products registered with FDA that contain talc as an ingredient were as follows:

014807966 TALC
2157

Talc is also a "batch certification-exempt" color additive that is approved (listed) for use in drug products (and as a substratum for certain drug and cosmetic color additive lakes), and talc may be safely used in such products in amounts consistent with good manufacturing practice to color drugs generally (21 CFR 73.1550); the listing regulation sets specifications for heavy metals (Pb ˜20 ppm; As ˜ 3 ppm)
Talc (sterile) is also approved by FDA under an NDA (21-388) for use as a sclerosing agent (intrapleural administration, pleuradesis), and I am also attaching to this note some information concerning that product.

Talc: Regulatory Status - Drugs, Cosmetics, Devices
There are no warning statements currently required in the codified regulations for talc as a cosmetic ingredient (21 CFR 740), nor are there prohibitions, restrictions, or requirements for tamper-resistant packaging of talc-containing cosmetic products (21 CFR 700).
In 1994, FDA-CFSAN/OCAC co-sponsored with the International Society of Regulatory Toxicology and Pharmacology (ISRTP) a 2-day Workshop on talc, which included presentations from the Agency (cosmetic and drug), industry, occupational, and academic (medical, public health) perspectives. The subjects covered in the Workshop included talc chemistry and characterization, regulatory history and issues, lung/pulmonary exposure, and Ovarian/Perineal Exposure Concerns. The annals of the Workshop were subsequently published in a peer-review journal:

"Talc: Consumer Uses and Health Perspectives", Regulatory Toxicology and Pharmacology, 21 (2), pp. 211-260 (April, 1995).

The several papers presented in the Workshop are provided for your convenience in .pdf (Adobe) format. In the paper by Dr. Gilbertson (FDA-CDER/DOTCDP) on "Regulatory Status", you will find that the issue of additional warnings because of accidental inhalation of baby powders was addressed in the context of the "Skin Protectant Drug Products Monograph" at the proposed rule stage; the issue of use on broken/ abraded skin was also addressed. I would recommend that you contact my colleague at FDA-OCAC, Mr. John Lipnicki, Team Leader, OCAC Regulations and Compliance Team, who may be able to help you further with additional citations, particularly with respect to the status of the final rulemaking. Also, Dr. Matthew Holman (FDA-CDER), who participated in CHIC-3 (Ottawa) can give you the very latest updates re. the status of proposed warnings for talc in OTC drug products categories regulated under the Monograph system.
Finally, with respect to cornstarch as a replacement for talc in 'talcum-type' powders, I would note that, while acute inhalation toxicity issues are always a concern with any fine powder used topically (particularly in an enclosed environment that is inadequately ventilated), cornstarch has some additional areas of potential concern, because of its biological/organic origins, which include microbial contamination (esp., bacterial spores) and potential flammability/explosiveness when the dust exceeds certain environmental thresholds.

I trust that this information is helpful. If there are other questions that you feel have not been sufficiently addressed, please feel free to contact our Office again, and I will be glad to provide additional information and guidance.

Best Personal Regards

Stan Milstein, OCAC

Stanley R. Milstein, Ph.D. (HFS-101)
Office of Cosmetics and Colors
Center for Food Safety and Applied Nutrition (CFSAN)
University Station Building (CPK2)
U.S. Food and Drug Administration (FDA)

4300 River Road
College Park, MD 20740
(Ph): 301 436-1343
(Fax): 301 436-2975
(E-mail): smilstei@cfsan.fda.gov

-----Original Message-----
From: Jennifer Butler [mailto:jennifer_butler@hc-sc.gc.ca]
Sent: Tuesday, August 09, 2005 1:03 PM
To: Stanley.Milstein@cfsan.fda.gov
Subject: Talcum powder

Hi Stanley,

I have a quick question. We are trying to develop a mandatory warning statement for the labels of Talc containing products. We are wondering if FDA has any such statement requirements for Talc products, Talcum powder and/ or corn starch. Of course, the primary concern is inhalation hazards associated with baby powders. Would you have any idea to which concentrations warnings should apply? Also, is exposure to broken or abraded skin a concern? Is any of this information in the Federal Register? If so, where could we find it? Any information is much appreciated.

Thank you in advance,

Jennifer Butler
Scientific Regulatory Officer
Consumer Product Safety Bureau
Cosmetics Division
Health Canada
P: (613) 948-3372
F: (613) 952-3039

From: Hansen, Patricia A
Sent: Tuesday, March 09, 2010 3:09 PM
To: Cianci, Sebastian M
Cc: Gasper, John; Meyers, Beth; Katz, Linda
Subject: FW: Press inquiry - talc

Seb,

Below are our answers. If the reporter has more questions, please forward them to Beth and me, with a cc to John Gasper (staff lead on the talc project). Thanks.

Pat

Patricia A. Hansen, Ph.D.
Sr. Advisor for Science and Policy
Office of Cosmetics and Colors, HFS-100

Tel.: 301-436-1130
Fax: 301-436-2975

1 FDA is conducting a survey of talc and talc-containing cosmetic products to help determine whether, and to what extent, cosmetic products in the U.S. marketplace may be contaminated with asbestos.
2 The current survey is being conducted because the most recent survey of talc in U.S. commerce was conducted many years ago and because there have been recent reports of asbestos-contaminated talc cosmetic products occurring overseas. (Asbestos, a known carcinogen, can be found in talc if the mining site is not carefully selected or if the talc ore is not sufficiently purified.)

3 The survey will use up-to-date laboratory techniques. (Details are not releasable at this time.)
4 The current work will be ongoing through 2010.
5 This survey is focused on asbestos.
6 We do not wish to speculate on what may be motivating the Cosmetic Ingredient Review. We suggest the reporter contact that group directly.
7 We have not received any reports of adverse events associated with talc.

From: Cianci, Sebastian M
To: Katz, Linda
Cc: Meyers, Beth
Sent: Mon Mar 08 17:37:36 2010
Subject: FW: Press inquiry - talc
Linda and Beth,

I received an inquiry from the Rose Sheet (Lauren Nardella). Lauren said she heard John Bailey talk about asbestos at the Personal Care Products Council annual meeting from a few weeks ago. She said John mentioned thatFDA is looking at analyzing talc for asbestos.

She has the following questions, but would really like an interview.

1. Why is FDA is looking into talc?

2. Was there something that prompted this?

3. What process/method are they using to analyze talc?

4. When do they expect to release results?

5. Is it specifically asbestos that that are looking at, or are there other aspects of talc that are of concern?

6. Is it merely coincidental that the Cosmetic Ingredient Review plans to review talc this year as well?

7. Can you tell me about any side effects resulting from exposure to talc in personal care products?

Her deadline is COB tomorrow so it might be faster to do an interview if you are ammenable to that.

Seb

Sebastian Cianci
Public Affairs Specialist
Trade Press Liaison
(301) 436-2291
Sebastian.Cianci@fda.hhs.gov

From: Nardella, Lauren (ELS-WSH) [mailto:L.Nardella@elsevier.com]
Sent: Monday, March 08, 2010 5:29 PM
To: Cianci, Sebastian M
Subject: RE: Press inquiry - talc
Thanks for the response!
I'm interested in learning, why is FDA is looking into talc?
Was there something that prompted this?
What process/method are they using to analyze talc?
When do they expect to release results?
Is it specifically asbestos that that are looking at, or are there other aspects of talc that are of concern?
Is it merely coincidental that the Cosmetic Ingredient Review plans to review

talc this year as well?
Can you tell me about any side effects resulting from exposure to talc in personal care products?

Thank you again Seb, I really appreciate your help!
- Lauren

Lauren Nardella
Reporter - "The Rose Sheet"
Elsevier Business Intelligence
5635 Fishers Lane
Suite 6000
Rockville, MD 20852
240-221-4456
www.therosesheet.com

From: Cianci, Sebastian M [mailto:Sebastian.Cianci@fda.hhs.gov]
Sent: Monday, March 08, 2010 5:23 PM
To: Nardella, Lauren (ELS-WSH)
Subject: RE: Press inquiry - talc

I'd be happy to help you out. What sort of questions do you have?

Sebastian

From: Nardella, Lauren (ELS-WSH) [mailto:L.Nardella@elsevier.com]
Sent: Monday, March 08, 2010 12:46 PM
To: Cianci, Sebastian M
Subject: Press inquiry - talc
Hi Seb,

Hope that all is well with you!

I'm working on a story following up on the Personal Care Products Council annual meeting from a few weeks ago. At the meeting, the Council's EVP of Science John Bailey mentioned that FDA is looking at analyzing talc for asbestos.

I was wondering if I might be able to interview someone at FDA regarding this. My deadline is end-of-day tomorrow.

Many thanks,
Lauren

Lauren Nardella
Reporter - "The Rose Sheet"
Elsevier Business Intelligence
5635 Fishers Lane
Suite 6000

Rockville, MD 20852
240-221-4456
www.therosesheet.com

Memorandum of Meeting

Date: March 22, 2010

Place: FDA, University Station, College Park, MD

Participants:

Visitors:
Rio Tinto: Judy Brown, Raga S. Elim
Barretts Minerals: Kevin D. Porterfield

FDA:
FDA: Linda M. Katz, M.D., M.P.H., Patricia A. Hansen, Ph.D., Robert L. Bronaugh, Ph.D., John Gasper J.D., Fred Hurley, Donald Havery

Subject: Talc

The meeting was held at the request of Rio Tinto, to discuss the January 27, 2010 and February 4, 2010 letters received by Rio Tinto and other talc producers/distributors. Specific issues from the letters that were to be addressed included the use of talc in cosmetics, the information FDA requested in the letters, and what FDA intended to do with the information.

FDA representatives described a general concern about the presence of asbestos in talc. This concern intensified when asbestos was reported last year in Chinese and Korean talc products. They also noted that FDA has limited information about the talc industry's testing procedures, acceptable asbestos levels, and specifications for "cosmetic grade" talc. Further, FDA has no specific data on the Chinese and Korean talc incidents except that the findings were "false positives."

FDA's letters were sent to talc producers listed in the International Cosmetic Ingredient Dictionary as an attempt to target the largest suppliers of "cosmetic" talc. FDA needs the requested information to assure that domestically produced and imported talc products that are sold to U.S. consumers are safe. Once FDA has collected the information requested, FDA will look into the feasibility of potentially issuing guidance to industry.

Industry representatives proposed a "workshop" setting where information on the talc industry could be exchanged rather than putting it in writing. This was later clarified to mean a meeting of those persons, including scientists, who could provide FDA the scientific background and detailed information on mineralogy, processing, and analytical methodology that would address FDA's questions posed in the letter to industry.

Industry representatives indicated that they did not have specific information on the Korean incident, but they were working with the Personal Care Products Council on talc standards and procedures for testing talc for asbestos. They indicated that the findings of asbestos in Chinese

talc were false positives. They offered to provide information on the specific issues and how they were resolved, the methods used, and measures to avoid false positives in the future.

Industry representatives suggested holding a meeting where scientific information could be exchanged. FDA was not adverse to this and suggested that industry will need to arrange for the meeting in writing, provide information on who should attend, and the subject areas to be covered. Industry representatives agreed to send FDA such a letter including an agenda, meeting objectives, and participants.

The Specialty Minerals/Barretts Minerals representative said they did not receive the original FDA letter but they would like to receive one officially. FDA representatives agreed to send them a letter.

Action items:

- FDA to send letter to Specialty Minerals
- Rio Tinto to request additional meeting in writing
- Rio Tinto to submit information to FDA on Chinese talc issues

Drafted: DHavery; 3/22/10
Rev/edit: LMKatz 3/22/10
Rev/edit: JGasper 3/22/10
Rev/edit: FHurley 3/22/10
Rev/edit: BBronaugh 4/19/10
Rev/edit: PHansen; 4/19/10
Rev/edit: LMKatz 4/21/10

From: Diallo, Mame K
To: Owens, Shirelle
Cc: Russ, Wanda
Subject: FW: Needed: Warning Labeling Talcum Power
Date: Monday, October 27, 2014 10:58:45 AM

Hi Shirelle,

I believe this is yours, please log in.

Thanks.

Mame

From: Russ, Wanda
Sent: Monday, October 27, 2014 8:54 AM
To: Diallo, Mame K
Subject: FW: Needed: Warning Labeling Talcum Power

Log in

Wanda Russ

From: Pennington, Caitlin
Sent: Monday, October 27, 2014 8:29 AM
To: Russ, Wanda
Cc: Palmer, Kelly; O'Neill, Jeff
Subject: FW: Needed: Warning Labeling Talcum Power

Caitlin

Caitlin M. Pennington
Program Support Specialist
Office of the Commissioner
Food & Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20903
Caitlin.Pennington@fda.hhs.gov
Office: 301-796-7064
BB: 301-518-4037

From: (b) (6) [mailto:(b) (6) t@earthlink.net]
Sent: Sunday, October 26, 2014 11:49 AM
To: Commissioner FDA
Subject: Needed: Warning Labeling Talcum Power

Ms. Hamburg:

I am writing regarding inadequate labeling of talcum powder (cosmetics) in U.S.

marketplace where distributors target female hygiene. This website Shower to Shower speaks
to this target advertising.

http://showertoshower.com/

Please don't wait any longer, require transparent labeling of the cosmetics industry about the smoking gun of talcum powder application for female genital hygiene. The FDA has rejected labeling requirements in the past.

I am (b) (6) have used talcum power my teenage and adult life – 45 years - because the ads and alleged safety. A year ago I was diagnosed with advanced (b) (6). I'm a non-smoker and there is no cancer in my family but I have used talc almost daily for personal hygiene all my life. Had I known there was a suspicion of risk (like tampons) I would have had a choice.

Failure to require warning labeling marginalizes the consumers, like myself, who fall into the "30% increase increase in ovarian cancer risk among female talc users" category (American Cancer Society webpage, below). Those of us in this category pay the ultimate price, as advanced ovarian cancer is 80% fatal.

The cosmetics industry will simply continue to "self-regulate" and reporting that their own tests are "inconclusive" which means it is big-money safe while they continue to target market to American female consumers. The target market is someone like me, their very own 45-yr lab rat. See two sources below from American Cancer Society and Ovarian Cancer Research Fund websites.

SOURCES

1- http://www.cancer.org/cancer/cancercauses/othercarcinogens/athome/talcum-powder-and-cancer

Excerpt from American Cancer Society website link above:

Studies in humans Ovarian cancer

It has been suggested that talcum powder might cause cancer in the ovaries if the powder particles (applied to the genital area or on sanitary napkins, diaphragms, or condoms) were to travel through the vagina, uterus, and fallopian tubes to the ovary. Several studies in women have looked at the possible link between talcum powder and cancer of the ovary. Findings are mixed, with some studies reporting a slightly increased risk and some reporting no increase.

For any individual woman, the overall increase in risk, if it exists, is likely to be small. For example, one analysis combining data from 16 studies published before 2003 found about a 30% increase in ovarian risk among talc users. The average woman's lifetime risk of ovarian cancer is about 1.4%, so even with a 30% increase, her lifetime risk would be about 1.8%. Still, talc is widely used in many products, so it is important to determine if the increased risk is real. Research in this area continues.

2- **http://www.ocrf.org/news/use-of-talc-based-powder-increases-ovarian-cancer-risk**

Excerpt from Ovarian Cancer Research Fund website link above:

Use of Talc-based Powder Increases Ovarian Cancer Risk

The use of talc-based powder has been associated with an increased risk of ovarian cancer in some, but not all, studies. In a new study published in *Cancer Prevention Research*, researchers found that "genital powder use is a modifiable exposure associated with small-to-moderate increases in risk of most histologic subtypes of epithelial ovarian cancer."

Examining data from thousands of women, the researchers found that genital powder was associated with a modest increased risk of epithelial ovarian cancer. There was no increase in risk among women who used the powder only on other parts of the body.

Thank you,

(b) (6)
[redacted]

State of Wisconsin
Governor Scott Walker

Department of Agriculture, Trade and Consumer Protection
Ben Brancel, Secretary

December 22, 2014

(b) (6)
[redacted]

RE: **File 576617** *(Refer to this number when contacting our agency)*
JOHNSON & JOHNSON INC
PO BOX 767
NEENAH WI 54957

Dear Ms Kilian:

Thank you for contacting the Department of Agriculture, Trade and Consumer Protection concerning Johnson & Johnson Inc.

I have written to the business to try to assist you to find a solution to your complaint. I asked them to review your concerns and then contact me to discuss what may be done to resolve your complaint. The company may also contact you directly.

In addition, some issues in your complaint may be within the authority of the agency listed below, so I am forwarding a copy of your complaint directly to them:

US FOOD AND DRUG ADMINISTRATION
US DEPARTMENT OF HEALTH AND HUMAN SERVICES
10903 NEW HAMPSHIRE AVE
SILVER SPRING MD 20993-0002

Telephone: 301 443-3170
Toll-free: 1-888-463-6332
www.fda.gov

Thank you again for bringing your complaint to our attention.

Sincerely,

Jeffery A. Schnetzler
Consumer Protection Investigator
Bureau of Consumer Protection
Voice Mail: 608 224-5178 Fax: 608 224-4677
E-Mail: Jeffery.Schnetzler@wisconsin.gov
www.facebook.com/wiconsumer

DATCP Hotline

From: (b) (6)
Sent: Friday, December 12, 2014 11:14 PM
To: DATCP Hotline
Subject: DATCP Web: Online Product Safety Complaint Form

Complaint or inquiry received via email/Internet by the Wisconsin Department of Agriculture, Trade, and Consumer Protection. This complaint and the information provided will be used in efforts to resolve the problem and will typically be shared with the party complained against. It may also be used to enforce applicable state laws. Under Wisconsin's Open Records Law, Wis. Stats. sec. 19.31, this complaint will be available for public review upon request.

Today's Date:	12/12/2014
Your information:	
Title:	(b) (6)
First name:	(b) (6)
Middle initial:	(b) (6)
Last name:	(b) (6)
Email address:	(b) (6)
Verify email address:	(b) (6)
Street address:	(b) (6)
Address line 2, or Apt #:	
PO Box:	
City:	(b) (6)
State:	(b) (6)
ZIP code:	(b) (6)
County:	(b) (6)
Home phone:	(b) (6)
Work phone:	
Cell phone:	(b) (6)
Phone me between 8:00 a.m. and 4:00 p.m. at:	Home
Best time to call:	12 pm-anytime

Information of victim if different from above:	
Title:	(b) (6)
First name:	((6)
Middle initial:	b (6)
Last name:	(b (6)
Email address:	
Street address:	
Address line 2, or Apt #:	
PO Box:	
City:	
State:	--Select--
ZIP code:	
County:	
Home phone:	
Work phone:	
Cell phone:	
Phone victim between 8:00 a.m. and 4:00 p.m. at:	
Best time to call:	
Your relationship to the victim:	Mother
Information about your complaint:	
Victim's Age:	21
Gender:	Female
Incident date?	
Product involved:	Johnson & Johnson Baby Talcum Powder
Product model:	
Serial number:	
Do you still have the product?	Yes
Brand name/manufacturer:	Johnson & Johnson

Manufacturer's address:	South building SK-255
Address line 2:	199 Grandview Road
City:	Skillman
State:	NJ
ZIP code:	08558-9901
Country:	USA
Manufacturer's email:	johnson&johnson.com
Manufacturer's website:	johnson&johnson.com
Manufacturer's contact person:	consumer products
Manufacturer's phone:	866-565-2229
Manufacturer's fax:	
Which of the following best describes your first contact with the business?	Radio or TV ad
Where was the product purchased?	Milwaukee
Date of purchase:	
Do you have a receipt?	No
Contact person at place of purchase:	
Phone number:	
Where did you pay the business?	At my home
Amount paid:	
Payment method:	Cash
Did you contact the manufacturer about your complaint?	Yes
Date you contacted manufacturer?	10/17/2014
What happened?	nothing
Have you filed this complaint with another agency?	No
Agency name:	
What happened?	
Have you contacted a private attorney?	Yes

Have you started court action?	No

Please describe the incident or hazard in detail and include a description of any injuries.

My daughter was diagnosed with 4th stage ovarian cancer in 2000 at age 18. She died 11-26-2002 at age 21. She used Johnson & Johnson Baby Talcum Powder from birth to her death. It came to my attention when I heard a tv ad telling how the connection to talcum powder and Ovarian Cancer is related and thousands of women have died from using their product.

Did the injury require medical treatment?	Yes
If yes, please describe:	from diagnosis to death hosptialized

How do you feel this complaint should be resolved?

This should be brought to the attention to the public. There are no warning labels to this date on any talcum products. There are numerous lawsuits pending. I could not hold them responsible because of the time limits of no remaining pathology slides since hospital records are not kept over 10 years. Nobody knows this because it has not brought to the public. Doctors are not aware Mothers are still using baby talc on female babies bottoms to this day. My god these findings are still being used on babies today without the dangers still not known. Somebody has to warn people and stop this company.

By submitting this form, I state that the information contained is true and accurate to the best of my knowledge.

From: Hemphill, Jennifer L
To: Meyers, Beth
Subject: 2015 Conference List
Date: Tuesday, December 16, 2014 11:51:43 AM
Attachments: Draft 2015 Exhibits w-estimated cost (4).docx

Jennifer L. Hemphill

FDA/CFSAN
Office of Analytics and Outreach
5100 Paint Branch Parkway
College Park, MD 20740
240-402-1907 (P)
301-436-2605 (F)

From: Hemphill, Jennifer L
To: Meyers, Beth
Subject: 2015 Conference List
Date: Tuesday, December 16, 2014 11:51:43 AM
Attachments: Draft 2015 Exhibits w-estimated cost (4).docx

Jennifer L. Hemphill

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